(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 June 2005 (16.06.2005)

PCT

(10) International Publication Number
WO 2005/054238 A1

(51) International Patent Classification[7]: C07D 471/04, A61K 31/41, A61P 35/00 // (C07D 471/04, 235:00, 221:00)

(21) International Application Number:
PCT/EP2004/013179

(22) International Filing Date:
19 November 2004 (19.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/524,214 21 November 2003 (21.11.2003) US

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CAPRARO, Hans-Georg** [CH/CH]; Habsburgerstrasse 60, CH-4310 Rheinfelden (CH). **FURET, Pascal** [FR/FR]; 24, rue du Riegelsbourg, F-68800 Thann (FR). **GARCIA-ECHEVERRIA, Carlos** [ES/CH]; Engelgasse 126, CH-4052 Basel (CH). **STAUFFER, Frédéric** [CH/CH]; Sonnenhofring 10, CH-4153 Reinach (CH).

(74) Agent: **GRUBB, Philip**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

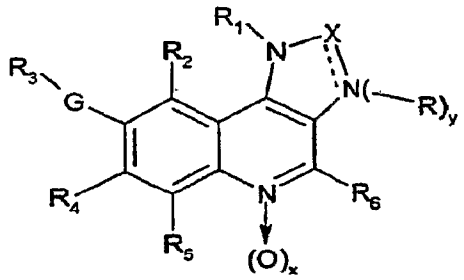
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/054238 A1

(54) Title: 1H-IMIDAZO[4,5-C]QUINOLINE DERIVATIVES IN THE TREATMENT OF PROTEIN KINASE DEPENDENT DISEASES



(57) Abstract: The invention relates to the use of imidazoquinolines and salts thereof in the treatment of protein kinase diseases and for the manufacture of pharmaceutical preparations for the treatment of said diseases, imidazoquinolines for use in the treatment of protein kinase dependent diseases, a method of treatment against said diseases, comprising administering the imidazoquinolines to a warm-blooded animal, especially a human, pharmaceutical preparations comprising an imidazoquinoline, especially for the treatment of a protein kinase dependent disease, novel imidazoquinolines, and a process for the preparation of the novel imidazoquinolines.

1*H*-Imidazo[4,5-c]quinoline derivatives in the treatment of protein kinase dependent diseases

The invention relates to the use of imidazoquinolines and salts thereof in the treatment of protein kinase dependent diseases and for the manufacture of pharmaceutical preparations for the treatment of said diseases, imidazoquinolines for use in the treatment of protein kinase dependent diseases, a method of treatment against said diseases, comprising administering the imidazoquinolines to a warm-blooded animal, especially a human, pharmaceutical preparations comprising an imidazoquinoline, especially for the treatment of a protein kinase dependent disease, novel imidazoquinolines, and a process for the preparation of the novel imidazoquinolines.

Background of the Invention

Recently, the concept of treating proliferative diseases by using drugs designed specifically against abnormally active protein kinases has been definitely proven in the treatment of chronic myeloid leukemia (CML) where a first product has now been approved for successful treatment. Clinical studies showed that the drug (*N*-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine, especially in the form of the methane sulfonate (monomesylate) salt called STI571, which is sold e.g. under the tradename Glivec®/Gleevec®, has impressive activity against chronic phase CML. Typical for CML is a characteristic t(9;22) translocation that juxtaposes the 5' end of the bcr gene with the 3' end of the abl gene, resulting in a unique 210 kDa fusion protein $p210^{bcr/abl}$ with constitutive kinase activity. The result is a $p210^{bcr/abl}$-induced transformation ultimately leading to CML. STI571 is a reversible inhibitor that occupies the ATP binding pocket of $p210^{bcr/abl}$ and stabilizes the kinase in an inactive conformation. This inhibitory action appears to be the basis for its action against CML.

Over-expression or constitutive expression (activity) of protein kinases appears to be a general principle for transformations that finally lead to proliferative growth of cells and thus cancer, psoriasis or other proliferative diseases.

Protein Kinase B (PKB, also known as Akt) is a member of a conserved family of kinases that includes PKBα, PKBβ, and PKBγ in humans. This serine/threonine kinase mediates the

physiological effects of several peptide growth factors, including platelet-derived growth factor, insulin, and insulin-like growth factor-I. PKB contains a pleckstrin homology (PH) domain in its amino-terminal domain, a kinase domain in the middle, and a regulatory domain in the carboxy-terminal region. The binding of phosphoinositides to the PH domain of PKB recruits PKB to the plasma membrane where it is phosphorylated on threonine-308/309 and on serine-473. Activation of the PKB pathways results in cellular proliferative, as well as antiapoptotic tumor cell responses. PKBα is amplified in 20% of gastric adenocarcinoma and PKBβ is amplified in 15% of ovarian cancers, 12% of pancreatic cancers, and 3% of breast carcinomas. PKBγ expression and activity is elevated in estrogen receptor negative breast cancer cells and in androgen-independent prostate cancer.

Compounds that down-regulate the kinase activity of PKB may prove to be of clinical interest for single and combined anticancer treatment modalities.

PDK1 (3-phosphoinosite-dependent protein kinase 1), which is a member of the AGC family of kinases, contributes to the activation of PKB by phosphorylating this protein at Thr-308/309 (the two numbers refer to the different protein isoforms). PDK1 kinase inhibitors could potentially have a therapeutic value by blocking the activation of the PKB mediated signal transduction pathways in cancer and other diseases such as Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome.

What is desirable from the point of view of possible treatments of proliferative diseases is to have a plethora of compound classes each tailored to specific protein kinases or protein kinase classes, thus allowing to come to specific treatments. Therefore, a strong need exists to find new classes of compounds allowing for such specific inhibitory effects.

Summary of the Invention

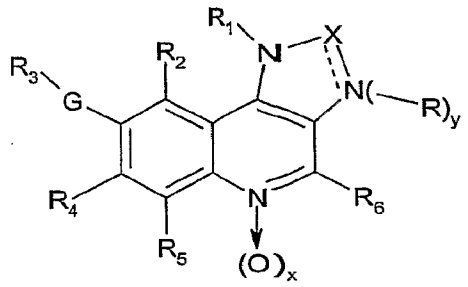
The class of imidazoquinoline compounds described herein, especially novel compounds falling under this class, has surprisingly been found to have pharmaceutically advantageous properties, *inter alia* allowing for the inhibition of specific types or classes or groups of protein kinases, especially PDK1, and as inhibitors of lipid kinases, in particular, phosphoinosite 3-kinases, or PI3K or Pi3. The class of imidazoquinoline compounds described herein also show inhibitory activity against KDR, PDGFR, c-Kit, Flt-3 and Flt-4.

The class of imidazoquinoline compounds described herein further inhibit mutants of said kinases.

In addition to this established activity, the imidazoquinolines have the advantage that their backbone in addition allows for a plethora of substitution patterns that offer a broad possibility to achieve a fine tuning for specific interaction with the ATP binding site of the targeted kinase or kinases, thus opening a new perspective and providing kinase inhibitors of various degrees of specificity.

Detailed Description of the Invention

The invention in particular relates to imidazoquinolines compounds of the formula (I)



(I)

wherein

each of x and y is, independently of the other, 0 or 1;

R_1 is an organic moiety that can be bound to nitrogen;

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond the with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen;

or X is (CR_7) wherein R_7 is hydrogen or an organic or inorganic moiety with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero or y is 1 and then -R is $\rightarrow$O;

G is unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene; and

each of R_2, R_3, R_4, R_5 and R_6 independently of the others, is hydrogen, an organic moiety or an inorganic moiety;

or pharmaceutically acceptable salts thereof,

and use of compounds of formula (I) in the treatment of protein kinase dependent diseases or for the manufacture of pharmaceutical preparations for the treatment of protein kinase dependent diseases.

The present invention also relates to a method of treating protein kinase dependent diseases comprising administering imidazoquinoline compounds of the formula (I) to a warm-blooded animal, especially a human. The present invention also relates to pharmaceutical preparations comprising an imidazoquinoline compound of the formula (I), especially for the treatment of a protein kinase dependent disease, novel imidazoquinoline compounds of the formula (I), a process for the manufacture of the novel imidazoquinoline compounds of the formula (I), and novel starting materials and intermediates for their manufacture. The present invention also relates to use of a compound of formula (I) in the manufacture of a pharmaceutical preparation for the treatment of a protein kinase dependent disease.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

The prefix "lower" denotes a radical having 1 up to and including a maximum of 7, especially 1 up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching. Lower alkyl, for example, is methyl, ethyl, *n*-propyl, *sec*-propyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *n*-hexyl or *n*-heptyl.

An organic moiety that can be bound to nitrogen is preferably unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted aryl-lower alkyl or aryl-lower alkoxy, unsubstituted or substituted heterocyclyl, unsubstituted or substituted heterocyclyl lower alkyl or lower alkoxy, unsubstituted or substituted cycloalkyl or unsubstituted or substituted cycloalkenyl.

An organic moiety is preferably unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl or unsubstituted or substituted cycloalkenyl, unsubstituted or substituted arylcarbonylamino, amino substituted by one or two moieties selected from the

group consisting of lower alkyl, substituted lower alkyl moieties, aryl, cycloalkyl and mercapto-lower alkyl, alkyloxy or cyano.

Halo or halogen is preferably fluoro, chloro, bromo or iodo, most preferably fluoro, chloro or bromo.

Alkyl preferably has up to 20, more preferably up to 12 carbon atoms and is linear or branched one or more times; preferred is lower alkyl, especially C_1-C_4alkyl. Alkyl may be linear or cyclic and can be unsubstituted or substituted, preferably by one or more substituents independently selected from those mentioned below under "substituted". Unsubstituted alkyl, preferably lower alkyl, or hydroxyalkyl, especially hydroxy-lower alky, e.g. 2-hydroxyethyl or cyclo-lower alky, e.g. cyclopropyl, is especially preferred as an organic moiety that can be bound to nitrogen.

Among the moieties corresponding to substituted alkyl, unsubstituted or substituted aryl-lower alkyl (especially preferred), heterocyclyl-lower alkyl, or cycloalkyl-lower alkyl are also preferred.

Aryl-lower alkyl is preferably lower alkyl that is substituted (preferably terminally or in 1-position) by unsubstituted or substituted aryl as defined below, especially phenyl-lower alkyl, such as benzyl or phenylethyl, especially 1-phenylethyl.

Heterocyclyl-lower alkyl is preferably lower alkyl that is substituted (preferably terminally) by unsubstituted or substituted heterocyclyl as defined below.

Cycloalkyl-lower alkyl is preferably lower alkyl that is substituted (preferably terminally) by unsubstituted or substituted cycloalkyl as defined below.

Alkenyl is preferably a moiety with one or more double bonds and preferably has 2-20, more preferably up to 12, carbon atoms; it is linear or branched one or more times (as far as possible in view of the number of carbon atoms). Preferred is C_2-C_7alkenyl, especially C_3-C_4alkenyl, such as allyl or crotyl. Alkenyl can be unsubstituted or substituted, especially by one or more, more especially up to three, of the substituents mentioned below under "substituted". Substituents such as amino or hydroxy (with free dissociable hydrogen) preferably are not bound to carbon atoms that participate at a double bond, and also other

substituents that are not sufficiently stable are preferably excluded. Unsubstituted alkenyl, in particular C_2-C_7alkenyl, is preferred.

When G is alkenylene, C_2-C_7alkenylene is preferred, with ethenylene (-C=C-) most preferred. When G is alkynylene, C_2-C_7alkynylene is preferred, with ethynylene (-C ≡C-) most preferred.

Alkynyl is preferably a moiety with one or more triple bonds and preferably has 2-20, more preferably up to 12, carbon atoms; it is linear of branched one or more times (as far as possible in view of the number of carbon atoms). Preferred is C_2-C_7alkynyl, especially C_3-C_4alkynyl, such as ethynyl or propyn-2-yl. Alkynyl can be unsubstituted or substituted, especially by one or more, more especially up to three, of the substituents mentioned below under "substituted". Substituents such as amino or hydroxy (with free dissociable hydrogen) preferably are not bound to carbon atoms that participate at a triple bond, and also other substituents that are not sufficiently stable are preferably excluded. Unsubstituted alkynyl, in particular C_2-C_7alkynyl, is preferred.

Aryl preferably has a ring system of not more than 20 carbon atoms, especially not more than 16 carbon atoms, is preferably mono-, bi- or tric-cyclic, and is unsubstituted or substituted preferably as defined below under "substituted". For example, aryl is selected from phenyl, naphthyl, indenyl, azulenyl and anthryl, and is preferably in each case unsubstituted or halo (especially fluoro, chloro, bromo or iodo); halo-lower alkyl (especially trifluoromethyl); sulfonamide (NH_2-$S(O)_2$-); dioxolo; hydroxy; amino; lower alkoxy (especially methoxy); hydroxy-lower alkyl (especially hydroxymethyl or 2-hydroxyethyl); mono or disubstituted amino; cyclic amino; amino-lower alkyl (especially aminomethyl, 2-aminoethyl or 3-aminopropyl); lower alkyl (especially methyl or ethyl); cyano; cyano-lower alkyl (especially 2-cyanoethyl); amidino; *N*-hydroxyamidino; amidino-lower alkyl (especially 2-amidino-ethyl); *N*-hydroxyamidino-lower alkyl (especially 2-(*N*-hydroxyamidino)-ethyl) substituted phenyl; or (especially 1- or 2-) naphthyl. Unsubstituted or substituted aryl, preferably phenyl; hydroxyphenyl (such as 4-hydroxyphenyl); methoxyphenyl (such as 2-, 3- or 4-methoxyphenyl); benzo[1,3]dioxolo; lower alkyl (such methyl or ethyl); is especially preferred as organic moiety that can be bound to nitrogen or as organic moiety R_2 to R_7.

In arylcarbonylamino, aryl is preferably aryl as defined in the last paragraph, especially benzoylamino.

Heterocyclyl is preferably a heterocyclic radical that is unsaturated, saturated or partially saturated in the bonding ring and is preferably a monocyclic or in a broader aspect of the invention bi- or tri-cyclic ring; has 3-24, more preferably 4-16 ring atoms; wherein at least in the ring bonding to the radical of the molecule of formula (I) one or more, preferably one to four, especially one or two carbon ring atoms are replaced by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, the bonding ring preferably having 4-12, especially 4-7 ring atoms; heteroaryl being unsubstituted or substituted by one or more, especially 1-4, substituents independently selected from the group consisting of the substituents defined below under "substituted"; especially being a heterocyclic radical selected from the group consisting of oxiranyl, azirinyl, 1,2-oxathiolanyl, imidazolyl, thienyl, furyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2*H*-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, pyranyol, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyridinyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, benzimidazolyl, cumaryl, indazolyl, triazolyl, tetrazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl, quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromanyl and chromanyl, each of these radicals being unsubstituted or substituted by one to two radicals selected from the group consisting of oxy, lower alkyl, especially methyl or *tert*-butyl, lower alkoxy, especially methoxy, and halo, especially fluoro or chloro. Unsubstituted or substituted heterocyclyl (e.g. morpholinyl, piperazinyl, lower alkyl piperazinyl, piperidino, piperidyl, pyrrolidinyl and azetidinyl) are preferred.

Cycloalkyl is preferably C_3-C_{10}cycloalkyl, especially cyclopropyl, dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, cycloalkyl being unsubstituted or substituted by one or more, especially 1-3, substituents independently selected from the group consisting of the substituents defined below under "substituted".

Cycloalkenyl is preferably C_5-C_{10}cycloalkenyl, especially cyclopentenyl, cyclohexenyl or cycloheptenyl, cycloalkenyl being unsubstituted or substituted by one or more, especially

1-3, substituents independently selected from the group consisting of the substituents defined below under "substituted".

An inorganic moiety R_2 to R_7 is preferably halogen, especially fluoro, chloro, bromo or iodo, hydroxy, amino, cyano or nitro.

An organic moiety R_2 to R_7 is selected from the organic moieties mentioned above for organic moieties that can be bound to nitrogen (for R_1) or is alternatively selected from the group consisting of unsubstituted or substituted alkoxy (e.g. lower alkoxy) or phenyl-lower alkoxy (e.g. methoxy); or lower alkanoyloxy (e.g. acetoxy); amino substituted by one or two moieties selected from the group consisting of lower alkyl (e.g.methyl, *n*-butyl, cyclopropyl or isopropyl); hydroxy-lower alkyl (e.g. 2-hydroxyethyl); mercapto-lower alkyl (e.g. 2-mercaptoethyl); unsubstituted or substituted C_5-C_{14}aryl, as defined above (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); a heteroaryl being unsubstituted or substituted by one or more, especially 1-3, substituents independently selected from the group consisting of the substituents defined below under "substituted"; especially being pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g. methoxy); halo (e.g. fluoro); or $-NR_8R_9$, wherein R_8 and R_9 can be the same or different and are independently H; lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl) or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl); cycloalkyl as defined above, especially C_3-C_6cycloalkyl; lower alkanoyl (preferably as single amino substituent or in combination with another of the non-acyl moiety just mentioned) and benzoyl or phenyl-lower alkanoyl (preferably as single amino substituent or in combination with another of the non-acyl moiety just mentioned); cyano; cyano-lower alkyl (such as cyanomethyl); amidino; *N*-hydroxyamidino; amidino-lower alkyl (such as –methyl); or *N*-hydroxyamidino-lower alkyl (such as –methyl).

Preferably, only up to five, more preferably up to two of R_2, R_3, R_4, R_5, R_6 and R_7 are/is other than hydrogen (that is, an inorganic or organic moiety).

A very preferred group of compounds of formula (I) are those wherein R_3 is one of the organic moieties other than hydrogen, especially those mentioned as being preferred above.

"Substituted", wherever used for a moiety, means that one or more hydrogen atoms in the respective moiety, especially up to five, more especially up to three, of the hydrogen atoms are replaced independently of each other by the corresponding number of substituents which preferably are independently selected from the group consisting of lower alkyl (e.g. methyl, ethyl or propyl); halo (e.g. F, Cl, Br or I); halo-lower alkyl (e.g. trifluoromethyl); hydroxy; carboxy; lower alkoxy (e.g. methoxy); phenyl-lower alkoxy; lower alkanoyloxy; lower alkanoyl; hydroxy-lower alkyl (e.g. hydroxymethyl or 2-hydroxyethyl); amino; mono or disubstituted amino; cyclic amino; amino-lower alkyl (e.g. aminomethyl, 2-aminoethyl or 3-aminopropyl); *N*-lower alkylamino; *N,N*-di-lower alkylamino; *N*-lower alkyl amino alkyl (e.g. methyl aminoethyl, cyclopropyl aminoethyl); *N,N*-di-lower alkyl amino alkyl; *N*-phenyl-lower alkylamino; *N,N-bis*(phenyl-lower alkyl)-amino; amino lower alkoxy (e.g. methoxy amino and methoxy *N*-methylamino); lower alkanoylamino; benzoylamino; carbamoyl-lower alkoxy; *N*-lower alkylcarbamoyl-lower alkoxy or *N,N*-di-lower alkylcarbamoyl-lower alkoxy; amidino; *N*-hydroxy-amidino; guanidine; amidino-lower alkyl (e.g. 2-amidinoethyl); *N*-hydroxyamidino-lower alkyl (e.g. *N*-hydroxy-amidino-methyl or –2-ethyl); carboxy; lower alkoxycarbonyl; phenyl; naphthyl; fluorenyl-lower alkoxycarbonyl (e.g. benzyloxycarbonyl); lower alkanoyl; sulfo; lower alkanesulfonyl (e.g. methanesulfonyl (CH_3-$S(O)_2$-)); sulfonamide (NH_2-$S(O)_2$-); *N*-lower alkyl sulfonamide alkyl (e.g. CH_3-NH_2- $S(O)_2$-alkyl); dioxolo; phosphono (-$P(=O)(OH)_2$); hydroxy-lower alkoxy phosphoryl or di-lower alkoxyphosphoryl; carbamoyl; mono- or di-lower alkylcarbamoyl; sulfamoyl; sulfamide; mono- or di-lower alkylaminosulfonyl; cyano-lower alkyl (e.g. cyanomethyl); C_5-C_{16}aryl (e.g. phenyl or naphthyl) where C_5-C_{16}aryl is substituted with any of the substituents defined above, and especially is phenyl which is unsubstituted or substituted with up to four, preferably up to three substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower alkoxy; amino-lower alkyl; *N*-lower alkyl amino alkyl (e.g. methyl aminoethyl, cyclopropyl aminoethyl); *N,N*-di-lower alkyl amino alkyl; amino-lower alkoxy; azetidinyl lower alkyl; pyrrolidinyl; amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted [e.g. -(C_1-C_7)NR_8R_9 or -O-(C_1-C_7)NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl), lower cycloalkyl (e.g. cyclopropyl) or R_8 and R_9 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)].

"Substituted" also includes: amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; amine heterocyclyl; heterocyclyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl; wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl, azetidinyl, pyridyl, piperidino, piperidyl, piperidinyl, piperazinyl, lower alkyl-piperazinyl, lower alkyl piperazinyl-lower alkyl, and substituted heterocyclyls such as pyrrolidin-2-one, oxazolidin-2-one, pyrrolidine-2,5-dione, piperazine-2-one and oxo-oxazolidinyl); C_3-C_{10}cycloalkyl (e.g. cyclopropyl or cyclohexyl); hydroxy-C_3-C_8cycloalkyl (e.g hydroxy-cyclohexyl); heteroaryl with 5 or 6 ring atoms and 1-4 ring heteroatoms selected from O, N and S, especially furyl and pyridyl; or -NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl) or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl). It goes without saying that substituents are only at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort which substitutions are possible and which are not. For example, amino or hydroxy groups with free hydrogen may be unstable if bound to carbon atoms with unsaturated (e.g. olefinic) bonds.

Salts are preferably the pharmaceutically acceptable salts of compounds of formula (I) if they are carrying salt-forming groups.

Salt-forming groups in a compound of formula (I) are groups or radicals having basic or acidic properties. Compounds having at least one basic group or at least one basic radical, for example, amino, a secondary amino group not forming a peptide bond or a pyridyl radical, may form acid addition salts, for example, with inorganic acids, such as hydrochloric acid, sulfuric acid or a phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example, aliphatic mono- or di-carboxylic acids, such as trifluoroacetic acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, malic acid, tartaric acid, citric acid or oxalic acid, or amino acids, such as arginine or lysine, aromatic carboxylic acids, such as benzoic acid, 2-phenoxy-benzoic acid, 2-acetoxy-benzoic acid, salicylic acid, 4-aminosalicylic acid, aromatic-aliphatic carboxylic acids, such as mandelic acid or cinnamic acid, heteroaromatic carboxylic acids, such as nicotinic acid or

isonicotinic acid, aliphatic sulfonic acids, such as methane-, ethane- or 2-hydroxyethanesulfonic acid, or aromatic sulfonic acids, for example, benzene-, *p*-toluene- or naphthalene-2-sulfonic acid. When several basic groups are present mono- or poly-acid addition salts may be formed.

Compounds of formula (I) having acidic groups, a carboxy group or a phenolic hydroxy group, may form metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example, sodium, potassium, magnesium or calcium salts, or ammonium salts with ammonia or suitable organic amines, such as tertiary monoamines, for example, triethylamine or tri-(2-hydroxyethyl)-amine, or heterocyclic bases, for example, *N*-ethyl-piperidine or *N,N'*-dimethylpiperazine. Mixtures of salts are possible.

Compounds of formula (I) having both acidic and basic groups can form internal salts.

For the purposes of isolation or purification, as well as in the case of compounds that are used further as intermediates, it is also possible to use pharmaceutically unacceptable salts, e.g. the picrates. Only pharmaceutically acceptable, non-toxic salts may be used for therapeutic purposes, however, and those salts are therefore preferred.

Owing to the close relationship between the novel compounds in free form and in the form of their salts, including those salts that can be used as intermediates, for example, in the purification of the novel compounds or for the identification thereof, any reference hereinbefore and hereinafter to the free compounds shall be understood as including the corresponding salts, where appropriate and expedient.

Where the plural form is used for compounds, salts, pharmaceutical preparations, diseases and the like, this is intended to mean also a single compound, salt, or the like.

Any asymmetric carbon atom may be present in the (*R*)-, (*S*)- or (*R,S*)-configuration, preferably in the (*R*)- or (*S*)-configuration. Substituents at a double bond or a ring may be present in *cis*- (= *Z*-) or trans (= *E*-) form. The compounds may thus be present as mixtures of isomers or preferably as pure isomers, preferably as enantiomer-pure diastereomers or pure enantiomers.

The present invention also relates to pro-drugs of a compound of formula (I) that convert *in vivo* to the compound of formula (I) as such. Any reference to a compound of formula (I) is

therefore to be understood as referring also to the corresponding pro-drugs of the compound of formula (I), as appropriate and expedient.

The terms "treatment" or "therapy" refer to the prophylactic or preferably therapeutic (including but not limited to palliative, curing, symptom-alleviating, symptom-reducing, kinase-regulating and/or kinase-inhibiting) treatment of said diseases, especially of the diseases mentioned below.

Where subsequently or above the term "use" is mentioned (as verb or noun) (relating to the use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof), this includes any one or more of the following embodiments of the invention, respectively: the use in the treatment of a protein kinase dependent disease, the use for the manufacture of pharmaceutical compositions for use in the treatment of a protein kinase dependent disease, methods of use of one or more compounds of the formula (I) in the treatment of a protein kinase dependent disease, the use of pharmaceutical preparations comprising one or more compounds of the formula (I) for the treatment of a protein kinase dependent disease, and one or more compounds of the formula (I) for use in the treatment of a protein kinase dependent disease, as appropriate and expedient and if not stated otherwise. In particular, diseases to be treated and are thus preferred for "use" of a compound of formula (I) are selected from protein kinase dependent ("dependent" meaning also "supported", not only "solely dependent") diseases mentioned herein, especially proliferative diseases mentioned herein, more especially any one or more of these or other diseases that depend on one or more of PDK1 or PI3K, or any combinations of these, or a mutant of any one or more of these, and a compound of the formula (I) can therefore be used in the treatment of a kinase dependent disease, especially a disease depending on one or more of the kinases mentioned above and below, where (especially in the case of aberrantly highly-expressed, constitutively activated and/or mutated kinases) said kinase-dependent disease is dependent on the activity of one or more of the said kinases or the pathways they are involved.

The compounds of formula (I) have valuable pharmacological properties and are useful in the treatment of protein kinase dependent diseases, for example, as drugs to treat proliferative diseases.

Preferred Embodiments of the Invention

With the groups of preferred compounds of formula (I) mentioned hereinafter, definitions of substituents from the general definitions mentioned hereinbefore may reasonably be used, for example, to replace more general definitions with more specific definitions or especially with definitions characterized as being preferred.

The invention relates especially to a compound of the formula (I),

wherein

each of x and y is, independently of the other, 0 or 1;

R_1 is an organic moiety that can be bound to nitrogen;

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond and with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen; or

X is (CR_7), wherein R_7 is hydrogen or an organic or inorganic moiety with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero or y is 1 and then -R is $\rightarrow$O;

G is unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene; and

each of R_2, R_3, R_4, R_5 and R_6, independently of the others, is an organic moiety or hydrogen or an inorganic moiety;

or a pharmaceutically acceptable salt thereof,

and its use in the treatment of a protein kinase dependent disease or for the manufacture of a pharmaceutical preparation for the treatment of a protein kinase dependent disease, or a method of treatment against said disease comprising administering a compound of the formula (I) to a warm-blooded animal, especially a human, in need of such treatment.

A tyrosine kinase dependent disease is preferably one depending on PDK1, PI3K and especially (aberrantly highly-expressed or activated) PKB/Akt (= PKB)-dependent disease or disease dependent on the activation of the PI3K/PKB pathway. The class of imidazoquinoline compounds described herein also show inhibitory activity against KDR, PDGFR, c-Kit, Flt-3 and Flt-4.

Also preferred is a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of, or preparation of a pharmaceutical composition for the treatment of, a protein kinase dependent disease, especially one depending on PDK1, PI3K and (especially aberrantly highly expressed or activated) PKB/Akt (= PKB)-dependent disease or disease dependent on the activation of the PI3K/PKB pathway.

Especially preferred is a compound of the formula (I), or a pharmaceutically acceptable salt thereof, wherein X is C=O or CR_7 and the other moieties are as defined under formula (I), for use in the diagnostic or therapeutic treatment of a warm-blooded animal, especially a human.

More preferred is a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein

each of x and y is, independently of the other, 0 or 1;

R_1 is substituted or unsubstituted aryl or heteroaryl especially phenyl, where the phenyl is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from: halo; cyano; cyano lower alkyl; lower alkyl; lower alkoxy; amino; amino-lower alkyl; amino-lower alkoxy; amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted [e.g. $-(C_1-C_7)NR_8R_9$ or $-O-(C_1-C_7)NR_8R_9$, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl, lower cycloalkyl or R_8 and R_9 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms]; amino-carbonyl-lower alkyl; heterocyclyl; heterocyclyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms; wherein alkyl may be linear or cyclic and the alkyl in any of the substituents above may optionally be substituted with $-NR_8R_9$, wherein R_8 and R_9 are as defined above;

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond and with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen; or

X is (CR_7), wherein R_7 is hydrogen or an organic moiety, such as C_1-C_7lower alkyl; amino or amino- lower-alkyl; wherein the alkyl may be unsubstituted or substituted with halo, lower alkoxy, or cycloalkyl with the proviso that then the dashed line bonding X

to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero, or y is 1 and then -R is $\rightarrow$O;

G is unsubstituted or substituted alkenylene; unsubstituted or substituted alkynylene;

R_2 is hydrogen;

R_3 is hydrogen lower alkyl; halo; lower alkoxy; unsubstituted or substituted C_5-C_{14}aryl; or a heteroaryl being unsubstituted or substituted by one or more, especially 1-4 substituents independently selected from the group consisting of the substituents defined above under "substituted"; especially being pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl, lower alkoxy, halo, or -NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl), lower cycloalkyl or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms;

R_4 is hydrogen or halo;

R_5 is hydrogen; and

R_6 is hydrogen, amino, amino-lower alkyl or alkylamido;

or a pharmaceutically acceptable salt thereof as such, especially for use in the preparation of a pharmaceutical composition, or for use in the diagnostic or therapeutic treatment of a warm-blooded animal, especially a human.

Especially preferred is a compound of formula (I),

wherein

each of x and y is, independently of the other, 0 or 1;

R_1 is substituted or unsubstituted phenyl where the phenyl is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower alkoxy; amino; amino-lower alkyl; amino-lower alkoxy; amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted, [e.g. -(C_1-C_7)NR_8R_9 or -O-(C_1-C_7)NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl), lower cycloalkyl (e.g. cyclopropyl) or R_8 and R_9 together with the N atom form a 3- to 8-membered

heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)]; amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; heterocyclyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl, azetidinyl, pyridyl, piperidino, piperidyl, piperazinyl or lower alkyl-piperazinyl); wherein alkyl may be linear or cyclic (e.g. cyclopropyl) and the alkyl in any of the substituents above may optionally be substituted with -NR_8R_9, wherein R_8 and R_9 are as defined above;

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond and with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen; or

X is (CR_7), wherein R_7 is hydrogen or an organic moiety, such as C_1-C_7lower alkyl; amino; amino-lower alkyl; wherein the alkyl may be unsubstituted or substituted with halo (e.g. methyl, ethyl, propyl, trifluoromethyl); lower alkoxy (e.g. methoxy); or cycloalkyl (e.g. cyclopropyl) with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero, or y is 1 and then -R is $\rightarrow$O;

G is unsubstituted or substituted alkenylene (e.g. ethenylene), unsubstituted or substituted alkynylene (e.g. ethynylene);

R_2 is hydrogen;

R_3 is hydrogen; lower alkyl; halo; (e.g. fluoro, chloro or bromo); lower alkoxy (e.g. methoxy) or unsubstituted or substituted C_5-C_{14}aryl, (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); or a heteroaryl being unsubstituted or substituted by one or more, especially 1-4, substituents independently selected from the group consisting of the substituents defined above under "substituted"; especially being pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g. methoxy); halo (e.g. fluoro); or -NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing

1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl);

R_4 is hydrogen or halo, (e.g. F or Cl);

R_5 is hydrogen; and

R_6 is hydrogen; amino; amino-lower alkyl or alkylamido (e.g. methylamido -NHC(O)-CH_3); or a pharmaceutically acceptable salt thereof as such, especially for use in the preparation of a pharmaceutical composition, or for use in the diagnostic or therapeutic treatment of a warm-blooded animal, especially a human.

Most especially preferred is a compound of formula (I),

wherein

each of x and y is, independently of the other, 0 or 1;

R_1 is substituted or unsubstituted phenyl where the phenyl is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower alkoxy; *N*-lower alkyl amino alkyl (e.g. methyl aminoethyl, cyclopropyl aminoethyl); *N,N*-di-lower alkyl amino alkyl; methoxy amino; methoxy N-methyl amino; amino; amino-lower alkyl; amino-lower alkoxy; azetidinyl lower alkyl; pyrrolidinyl; *N*-lower alkyl sulfonamide alkyl (e.g. CH_3-NH_2- $S(O)_2$-alkyl); amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted, [e.g. -(C_1-C_7)NR_8R_9 or -O-(C_1-C_7)NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl), lower cycloalkyl (e.g. cyclopropyl) or R_8 and R_9 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)]; amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; heterocyclyl-lower alkyl; lower alkyl piperazinyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl, azetidinyl, pyridyl, piperidino, piperidyl, piperazinyl or lower alkyl-piperazinyl); substituted heterocyclyls such as pyrrolidin-2-one, oxazolidin-2-one, pyrrolidine-2,5-

dione, piperazine-2-one and oxo-oxazolidinyl; wherein alkyl may be linear or cyclic (e.g. cyclopropyl) and the alkyl in any of the substituents above may optionally be substituted with $-NR_8R_9$, wherein R_8 and R_9 are as defined above;

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond and with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen; or

X is (CR_7), wherein R_7 is hydrogen or an organic moiety, such as C_1-C_7lower alkyl; amino; amino-lower alkyl; wherein the alkyl may be unsubstituted or substituted with halo (e.g. methyl, ethyl, propyl, trifluoromethyl); lower alkoxy (e.g. methoxy); or cycloalkyl (e.g. cyclopropyl) with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero, or y is 1 and then -R is $\rightarrow$O;

G is unsubstituted or substituted alkenylene (e.g. ethenylene), unsubstituted or substituted alkynylene (e.g. ethynylene);

R_2 is hydrogen;

R_3 is hydrogen; lower alkyl; halo (e.g. fluoro, chloro or bromo); lower alkoxy (e.g. methoxy); unsubstituted or substituted C_5-C_{14}aryl (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); or a heteroaryl being unsubstituted or substituted by one or more, especially 1-4, substituents independently selected from the group consisting of the substituents defined above under "substituted"; especially being pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g. methoxy); halo (e.g. fluoro); or $-NR_8R_9$, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl) or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl);

R_4 is hydrogen or halo, (e.g. F or Cl);

R_5 is hydrogen; and

R_6 is hydrogen; amino; amino-lower alkyl or alkylamido (e.g. methylamido -NHC(O)-CH_3);

or a pharmaceutically acceptable salt thereof as such,

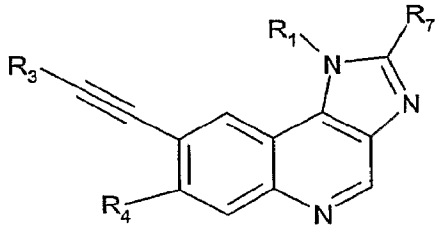
especially for use in the preparation of a pharmaceutical composition, or for use in the diagnostic or therapeutic treatment of a warm-blooded animal, especially a human.

Especially preferred is a compound of formula (I) for use in the treatment of a protein kinase dependent disease or for the manufacture of a pharmaceutical preparation for the treatment of a protein kinase dependent disease, or a method of treatment against said disease, comprising administering a compound of the formula (I) to a warm-blooded animal, especially a human, in need of such treatment.

Especially preferred is a compound of formula (I) for use in the treatment of a proliferative disease selected from a benign or malignant tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, a mammary carcinoma or a leukemia. Other diseases include Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome.

Having regard to their inhibition of phosphatidylinositol 3-kinase enzymes, compounds of formula (I) in free or pharmaceutically acceptable salt form, are useful in the treatment of conditions which are mediated by the activation of the PI3K kinase enzymes, particularly inflammatory or allergic conditions. Treatment in accordance with the invention may be symptomatic or prophylactic. Other preferred embodiments include pharmaceutical composition comprising a compound according to formula (I), and pharmaceutical compositions comprising a pharmaceutically acceptable carrier material.

Another embodiment of the present invention relates to a compound of formula (Ia)



(Ia)

wherein R_1, R_3, R_4 and R_7 are as defined above.

Most preferred is a compound of formula (Ia) wherein

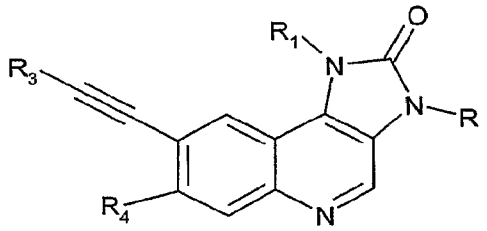
R_1 is substituted or unsubstituted aryl or heteroaryl, especially phenyl which is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower alkoxy; amino-lower alkyl; amino-lower alkoxy; amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted, [e.g. -(C_1-C_7)NR_8R_9 or -O-(C_1-C_7)NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl), lower cycloalkyl (e.g. cyclopropyl) or R_8 and R_9 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)]; amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; heterocyclyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl, azetidinyl, pyridyl, piperidino, piperidyl, piperazinyl or lower alkyl-piperazinyl); wherein alkyl may be linear or cyclic (e.g. cyclopropyl) and the alkyl in any of the substituents above may optionally be substituted with -NR_8R_9, wherein R_8 and R_9 are as defined above;

R_3 is hydrogen; lower alkyl; halo (e.g. fluoro, chloro or bromo); lower alkoxy (e.g. methoxy); unsubstituted or substituted C_5-C_{14}aryl (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); or a heteroaryl being unsubstituted or substituted by one or more, especially 1-4, substituents independently selected from the group consisting of the substituents defined above under "substituted"; especially being pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g. methoxy); halo (e.g. fluoro); or -NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl);

R_4 is hydrogen or halo, especially fluoro; and

R_7 is hydrogen or an organic moiety, such as C_1-C_7 lower alkyl, amino or amino-lower alkyl; wherein the alkyl may be unsubstituted or substituted with halo (e.g. methyl, ethyl, propyl, trifluoromethyl); lower alkoxy (e.g. methoxy); or cycloalkyl (e.g. cyclopropyl); or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention relates to a compound of formula (Ib)



(Ib)

wherein R_1, R_3, R_4, R and y are as defined above.

Most preferred is a compound of formula (Ib),

wherein

R_1 is substituted or unsubstituted aryl or heteroaryl, especially phenyl which is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower alkoxy; amino; amino-lower alkyl; amino-lower alkoxy; amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted, [e.g. -(C_1-C_7)NR_8R_9 or -O-(C_1-C_7)NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl), lower cycloalkyl (e.g. cyclopropyl) or R_8 and R_9 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)]; amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; heterocyclyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl, azetidinyl, pyridyl, piperidino, piperidyl, piperazinyl or lower alkyl-piperazinyl); wherein alkyl may be linear or cyclic

(e.g. cyclopropyl) and the alkyl in any of the substituents above may optionally be substituted with $-NR_8R_9$, wherein R_8 and R_9 are as defined above;

R_3 is hydrogen; lower alkyl; halo (e.g. fluoro, chloro or bromo); lower alkoxy (e.g. methoxy); unsubstituted or substituted C_5-C_{14}aryl (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); or a heteroaryl being unsubstituted or substituted by one or more, especially 1-3, substituents independently selected from the group consisting of the substituents defined above under "substituted"; especially being pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g. methoxy); halo (e.g. fluoro); or $-NR_8R_9$, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl);

R_4 is hydrogen or halo, especially fluoro; and

R is hydrogen or substituted or unsubstituted C_1-C_7 lower alkyl, aryl, heteroaryl, amino, mono or disubstituted amino, lower alkoxy e.g. OCH_3 or cycloalkyl, e.g. cyclopropyl;

or a pharmaceutically acceptable salt thereof.

Also preferred is a compound of the formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in the preparation of a pharmaceutical composition, or for use in the treatment of a protein kinase dependent disease, especially one depending on PDK1, PI3K and (especially aberrantly highly-expressed or activated) PKB/Akt (= PKB)-dependent disease or a disease dependent on the activation of the PI3K/PKB pathway.

Especially preferred is a compound of the formula (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, wherein X is C=O or CR_7 and the other moieties are as defined under formula (I), for use in the preparation of a pharmaceutical composition, or for use in the diagnostic or therapeutic treatment of a warm-blooded animal, especially a human.

Very preferred is the use of a compound according to formula (I), (Ia) or (Ib), where the disease to be treated is a proliferative disease or conditions which are mediated by the activations of PI3K kinase enzymes, particularly inflammatory or allergic conditions.

Most preferred is the use in accordance with the present invention of a compound of the formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, as exemplified below under 'Examples'.

Especially preferred is a novel compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, for use in the therapeutic or diagnostic treatment of a warm-blooded animal, especially a human; or the use of such a novel compound of formula (I), (Ia) or (Ib), or a pharmaceutically acceptable salt thereof, in the treatment of a protein kinase dependent disease or for the manufacture of a pharmaceutical preparation for the treatment of said disease.

Most special preference is further given to the novel compounds of formula (I), (Ia) or (Ib) mentioned in the examples below, or a salt, especially a pharmaceutically acceptable salt, thereof.

PDK1 inhibition can be measured as follows: *Cloning and expression*: pCMV-GST-PDK1 (G Thomas, FMI Basel, as described in Pullen, N. et al., Science, 279:707-710 (1998)) is digested with EcoR1 and Sma1 to release a DNA fragment encoding amino acids 52-556 of PDK1. This is subsequently ligated to the vector pFB-G01-GST1 with compatible ends achieved by restriction digestion with EcoR1 and Stu1. The ligation reaction is transformed into XL-1 Blue bacteria and plated on selective LB agar. Resultant colonies are cultured overnight, plasmid DNA extracted and restriction analysed. Colonies that are found to contain plasmids with the correct insert are taken for large-scale plasmid preparation and subsequent sequence analysis to confirm the expected plasmid sequence.

Production of virus: Transfer vectors containing the kinase domain of PDK1 are transfected into the DH10Bac cell line (GIBCO) and the cells are plated on selective agar plates. Colonies without insertion of the fusion sequence into the viral genome (carried by the bacteria) are blue. Single, white colonies are picked and viral DNA (bacmid) is isolated from the bacteria by standard plasmid purification procedures. Sf9 cells or Sf21 cells (American

Type Culture Collection) are then transfected in 25 cm^2 flasks with the viral DNA using Cellfectin reagent.

Protein expression in Sf9 cells: Virus-containing media is collected from the transfected cell culture and used for infection to increase its titer. Virus-containing media obtained after two rounds of infection is used for large-scale protein expression. For large-scale protein expression 100 cm^2 round tissue culture plates are seeded with 5 x 10^7 cells/plate and infected with 1 mL of virus-containing media (approx. 5 MOIs). After 3 days, the cells are scraped off the plate and centrifuged at 500 rpm for 5 minutes. Cell pellets from 10-20, 100 cm^2 plates are resuspended in 50 mL of ice-cold lysis buffer (25 mM Tris-HCl, pH 7.5, 2 mM EDTA, 1% NP-40, 1 mM DTT, 1 mMP MSF). The cells are stirred on ice for 15 minutes and then centrifuged at 5,000 rpms for 20 minutes.

Purification of GST-tagged proteins: The centrifuged cell lysate is loaded onto a 2 mL glutathione-sepharose column (Pharmacia) and washed 3 x with 10 mL of 25 mM Tris-HCl, pH 7.5, 2 mM EDTA, 1 mM DTT, 200 mM NaCl. The GST-tagged proteins are then eluted by 10 applications (1 mL each) of 25 mM Tris-HCl, pH 7.5, 10 mM reduced-glutathione, 100 mM NaCl, 1 mM DTT, 10% glycerol and stored at -70°C.

Measure of enzyme activity: Tyrosine protein kinase assays with purified GST-PDK1 are carried out in a final volume of 30 µL containing 100 ng of enzyme protein, 50 mM HEPES, pH 7.6, 10 mM $MgCl_2$, 1 mM DTT, 10 µM Na_3VO_4, 100 µg/mL casein, 1% DMSO, 0.1 mM EGTA, pH 8.0, 10.0 µM ATP and 0.1 µCi [γ-^{33}P] ATP. The activity is assayed in the presence or absence of inhibitors [compounds of formula (I)] by measuring the incorporation of ^{33}P from [γ^{33}P] ATP into appropriate substrates. The assay is carried out in 96-well plates at ambient temperature for 30 minutes under conditions described below and terminated by the addition of 20 µL of 125 mM EDTA. Subsequently, 40 µL of the reaction mixture are transferred onto Immobilon-PVDF membrane (Millipore) previously soaked for 5 minutes with methanol, rinsed with water, then soaked for 5 minutes with 0.5% H_3PO_4 and mounted on vacuum manifold with disconnected vacuum source. After spotting all samples, vacuum is connected and each well-rinsed with 200 µL 0.5% H_3PO_4. Membranes are removed and washed 4 x on a shaker with 1.0% H_3PO_4, once with ethanol. Membranes are counted after drying at ambient temperature, mounting in Packard TopCount 96-well frame, and addition of 10 µL/well of Microscint TM (Packard). IC_{50} values of compounds of formula (I) are calculated by linear regression analysis of the percentage inhibition of each compound in

duplicate, at four concentrations (usually 0.01, 0.1, 1 and 10 µM). One unit of protein kinase activity is defined as 1 nmole of ^{33}P ATP transferred from [$\gamma^{33}P$] ATP to the substrate protein/minute/mg of protein at 37°C.

The compounds of the formula (I) are found to show IC_{50} values for PDK1 inhibition in the range from 0.001-20 µM, preferably in the range from 0.01-2 µM.

Detection of phospho-PKB and phospho-GSK3β is as follows: On day 1, U87MG cells (ATCC No. HTB-14) are trypsinized, counted in a Neubauer chamber, and diluted in fresh complete RPMI 1640 medium to a final concentration of 6 x 10^5 cells/mL. Ten (10) cm tissue culture dishes are then loaded with 10 mL of the cell suspension, and incubated for 18 hours.

On day 2, the medium in plates is discarded and replaced by complete RPMI 1640 medium containing either DMSO or inhibitors [compounds of formula (I)]. After 30 minutes of contact, the medium is quickly removed by aspiration and the cells rinsed twice with pre-cooled PBS. Cells are then placed on ice and immediately lysed. Protein samples are then resolved by SDS-PAGE and transferred to Immbilon-P membrane for detection of levels of endogenous GSK3β, PKB, PhosphoT308-PKB and PhosphoS9-GSK3β by western-blotting. Membranes are then dried and covered with polyethylene film, and chemiluminescence measured in a MultiImage™ Light Cabinet (Alpha Innotech Corp) driven with the FluorChem™ software (Alpha Innotech Corp).

The data are analyzed with AphaEasy software, plotted as % of control (cells treated with DMSO in identical experimental conditions used for kinase inhibitors) with SigmaPlot® (SSPI Inc, version 7) as a regression curve (Four Parameter Logistic Cubic) and IC_{50} values are determined accordingly.

IC_{50} calculations

input	3 x 4 µl stopped assay on Immobilon membrane, not washed
background (3 wells)	assay with H_2O instead of enzyme.
positive control (4 wells)	3 % DMSO instead of compound
bath control (1 well)	no reaction mix

IC_{50} values are calculated by logarithmic regression analysis of the percentage inhibition of each compound at 4 concentrations (usually 3- or 10-fold dilution series starting at 10 µM).

In each experiment, the actual inhibition by reference compound is used for normalization of IC_{50} values to the basis of an average value of the reference inhibitor:

$$\text{Normalized } IC_{50} = \text{measured } IC_{50} \cdot \text{average ref. } IC_{50} / \text{measured ref. } IC_{50}$$

Example: Reference inhibitor in experiment 0.4 µM, average 0.3 µM
Test compound in experiment 1.0 µM, normalization: 0.3/0.4 = 0.75 µM

For example, staurosporine or a synthetic staurosporine derivative are used as reference compounds.

Using this protocol, the compounds of the formula (I) are found to show IC_{50} values for PDK1 inhibition in the range from 0.001-20 µM, preferably in the range from 0.01-2 µM.

Compounds of formula I and their pharmaceutically acceptable salts are useful as pharmaceuticals. In particular, they exhibit inhibition of phosphatidylinositol 3-kinase (PI3K kinase) enzymes, especially the gamma isoform (p110γ), which are responsible for generating phosphorylated signalling products. The inhibitory properties of compounds of formula I may be demonstrated in the following test procedures:

Baculovirus expressing different fragments of PI3Kγ fused to GST have been previously described by Stoyanova et al. (1997) Lipid- and protein kinase activities of G protein-coupled PI 3-kinase g: structure-activity analysis and interactions with wortmannin. *Biochem. J.*, 324:489. Residues 38-1102 of human PI3Kγ are subcloned into the BamH1 and EcoR1 sites of the transfer vector pAcG2T (Pharmingen) to create a GST-PI3Kγ lacking the first 37 residues of PI3Kγ. To express the recombinant protein, Sf9 (*Spodoptera frugiperda* 9) insect cells are routinely maintained at densities between 3 X 10^5 and 3 X 10^6 cells/ml in serum containing TNMFH medium (Sigma). Sf9 cells, at a density of 2 X 10^6 are infected with human GST-PI3KγΔ34 baculovirus at a multiplicity of infection (m.o.i.) of 1 for 72 hours. The infected cells are harvested by centrifugation at 1400 g for 4 minutes at 4° C and the cell pellets are frozen at -80° C. Both Sf9 and Sf21 cells work equally well. Sf9 cells (1X10^9) are resuspended in 100 ml cold (4° C) lysis buffer (50 mM Tris-HCl pH 7.5, 1% Triton X-100, 150 mM NaCl, 1 mM NaF, 2 mM DTT and protease inhibitors. Cells are incubated on ice for 30 minutes then centrifuged at 15000 g for 20 minutes at 4° C. Purification of the supernatant sample is carried out at 4° C by affinity chromatography using SEPHAROSE™ agarose gel beads coupled to glutathione (from Amersham Pharmacia Biotech). A cell lysate/GST resin

ratio of 50:1 is used. The GST resin is firstly pre-rinsed to remove ethanol preservative and then equilibrated with lysis buffer. Cell lysate (supernatant) is added (usually as 50 ml lysate to 1 ml GST resin in 50 ml tubes) and gently rotated on a mixer at 4° C for 2-3 hours. The unbound flow through sample is collected by centrifugation at 1000g for 5 minutes at 4° C using a DENLEY™ centrifuge. The 1 ml GST resin containing bound material is transferred to a 15 ml FALCON™ centrifuge tube for subsequent washing and elution steps. Firstly a series of 3 cycles of washings (mixing by gentle inversion) is performed with 15 ml ice cold wash Buffer A (50 mM Tris-HCl pH 7.5, 1% Triton X-100, 2 mM DTT) interspersed with centrifugation at 1000g for 5 minutes at 4° C. A final single wash step is performed with 15 ml ice cold wash Buffer B (50mM Tris-HCl pH 7.5, 2 mM DTT) and then centrifuged at 1000g for 5 minutes at 4° C. The washed GST resin is finally eluted with 4 cycles of 1 ml ice cold elution buffer (50 mM Tris-HCl pH 7.5, 10 mM reduced glutathione, 2 mM DTT, 150 mM NaCl, 1 mM NaF, 50% ethylene glycol and protease inhibitors) interspersed with centrifugation at 1000g for 5 minutes at 4° C. Samples are aliquoted and stored at -20° C.

An in vitro kinase assay was established that measures the transfer of the terminal phosphate of adenosine triphosphate to phosphatidylinositol. The kinase reaction is performed in a white 96 well microtitre plate as a Scintillation Proximity Assay. Each well contains 10 µl test compound in 5% dimethylsulphoxide and 20 µl assay mix (40 mM Tris, 200 mM NaCl, 2 mM ethyleneglycol-aminoethyl-tetraacetic acid (EGTA), 15 µg/ml phosphatidylinositol, 12.5 µM adenosine triphosphate (ATP), 25 mM $MgCl_2$, 0.1 µCi [^{33}P]ATP). The reaction is started by the addition of 20 µl of enzyme mix (40 mM Tris, 200 mM NaCl, 2 mM EGTA containing recombinant GST-p110γ). The plate is incubated at room temperature for 60 minutes and the reaction terminated by the adding 150 µl of WGA-bead stop solution (40 mM Tris, 200 mM NaCl, 2 mM EGTA, 1.3 mM ethylene diamine tetraacetic acid (EDTA), 2.6 µM ATP and 0.5 mg of Wheat Germ Agglutinin-SPA beads (Amersham Biosciences) to each well. The plate is sealed, incubated at room temperature for 60 minutes, centrifuged at 1200 rpm and then counted for 1 minute using a scintillation counter. Total activity is determined by adding 10 µl of 5% dimethylsulphoxide (DMSO) and non-specific activity is determined by adding 10 µl 50 mM EDTA in place of the test compound.

The compounds of formula (I) that inhibit the protein kinase activities mentioned, especially tyrosine and/or the serine/threonine protein kinases mentioned above, can therefore be used in the treatment of protein kinase dependent diseases, especially diseases depending on

PDK1 kinases activity. Protein kinase dependent diseases are especially proliferative diseases, preferably a benign or especially malignant tumor, more preferably carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach (especially gastric tumors), ovaries, colon, rectum, prostate, pancreas, lung, vagina, thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, or a tumor of the neck and head, an epidermal hyperproliferation, especially psoriasis, prostate hyperplasia, a neoplasia, especially of epithelial character, preferably mammary carcinoma, or a leukemia. They are able to bring about the regression of tumors and to prevent the formation of tumor metastases and the growth of (also micro) metastases. In addition they can be used in epidermal hyperproliferation (e.g. psoriasis), in prostate hyperplasia, in the treatment of neoplasias, especially of epithelial character, for example, mammary carcinoma, and in leukemias. It is also possible to use the compounds of formula (I) in the treatment of diseases of the immune system insofar as several or, especially, individual tyrosine protein kinases and/ or (further) serine/threonine protein kinases are involved; furthermore, the compounds of formula (I) can be used also in the treatment of diseases of the central or peripheral nervous system where signal transmission by at least one tyrosine protein kinase and/or (further) serine/threonine protein kinase is involved.

Especially compounds of formula (I) that show inhibition of PDK1 kinase are useful in the treatment of PTEN negative cancers or cancers that overexpress PKB or PI3K or diseases associated with deregulation of the PI3K/PKB pathway.

Further, compounds of the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyper-reactivity, remodelling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (This particular asthmatic condition is commonly referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyper-reactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyper-reactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, cystic fibrosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, compounds of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hyper-eosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome),

eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

Compounds of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

Compounds of the present invention may also be used for the treatment of other diseases or conditions, in particular diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or aetiology, including autoimmune haematological disorders (e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary billiary cirrhosis, uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy).

Other diseases or conditions which may be treated with compounds of the invention include septic shock, rheumatoid arthritis, osteoarthritis, proliferative diseases such as cancer, atherosclerosis, allograft rejection following transplantation, stroke, obesity, restenosis, diabetes, e.g. diabetes mellitus type I (juvenile diabetes) and diabetes mellitus type II, diarrhoeal diseases, ischemia/reperfusion injuries, retinopathy, such as diabetic retinopathy or hyperbaric oxygen-induced retinopathy, and conditions characterised by elevated intraocular pressure or secretion of ocular aqueous humor, such as glaucoma.

The effectiveness of compounds of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e.g. a mouse or rat model, of airways inflammation or other inflammatory conditions, for example as described by Szarka et al, *J. Immunol. Methods* (1997) 202:49-57; Renzi et al, *Am. Rev. Respir. Dis.* (1993) 148:932-939; Tsuyuki et al., *J. Clin. Invest.* (1995) 96:2924-2931; and Cernadas et al (1999) *Am. J. Respir. Cell Mol. Biol.* 20:1-8.

There are also experiments to demonstrate the antitumor activity of compounds of the formula (I) *in vivo*.

Female Harlan athymic nu/nu mice with s.c. transplanted human glioblastoms U87MG tumors can be used to determine the anti-tumor activity of PDK1 kinase inhibitors. On day 0, with the animals under peroral forene narcosis, a tumor fragment of approximately 25 mg is placed under the skin on the animals' left flank and the small incised wound is closed by means of suture clips. When tumors reaches a volume of 100 mm^3 the mice are divided at random into groups of 6-8 animals and treatment commences. The treatment is carried out for a 2-3 weeks period with peroral, intravenous or intra-peritoneal administration once daily (or less frequently) of a compound of formula (I) in a suitable vehicle at defined doses. The tumors are measured twice a week with a slide gauge and the volume of the tumors is calculated.

As an alternative to cell line U87MG, other cell lines may also be used in the same manner, for example,

- the MDA-MB 468 breast adenocarcinoma cell line (ATCC No. HTB 132; see also In Vitro 14, 911-15 [1978]);
- the MDA-MB 231 breast carcinoma cell line (ATCC No. HTB-26; see also In Vitro 12, 331 [1976]);
- the MDA-MB 453 breast carcinoma cell line (ATCC No.HTB-131);
- the Colo 205 colon carcinoma cell line (ATCC No. CCL 222; see also Cancer Res. 38, 1345-55 [1978]);
- the DU145 prostate carcinoma cell line DU 145 (ATCC No. HTB 81; see also Cancer Res. 37, 4049-58 [1978]),
- the PC-3 prostate carcinoma cell line PC-3 (especially preferred; ATCC No. CRL 1435; see also Cancer Res. 40, 524-34 [1980]) and the PC-3M prostate carcinoma cell line;

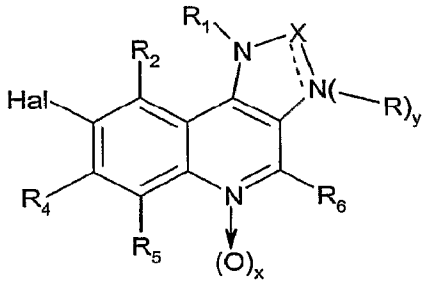
- the A549 human lung adenocarcinoma (ATCC No. CCL 185; see also Int. J. Cancer 17, 62-70 [1976]),
- the NCI-H596 cell line (ATCC No. HTB 178; see also Science 246, 491-4 [1989]);
- the pancreatic cancer cell line SUIT-2 (see Tomioka et al., Cancer Res. 61, 7518-24 [2001]).

Other cell lines include gioblastoma cell lines that are PTEN negative (see Ishii et al., Brain Pathology 9, 469-479 [1999]), such as

- LN-71;
- LN-215;
- LN-235.

The compounds of the formula (I) can be prepared according to the following methods:

In one preferred embodiment, a compound of formula (I) is prepared by reacting a compound of the formula (II)



(II)

with an alkenylene or alkynylene derivative, preferably phenylethylene boronic acid, phenylacetylene, 3-methoxyphenylacetylene, 4-methoxyphenylacetylene, 3-ethynylpyridine, 5-ethynyl-2-methoxy-pyridine, 5-ethynyl-benzo[1,3]dioxolo or 4-ethynyl-benzenesulfonamide, wherein

Hal refers to halogen preferably bromine; and

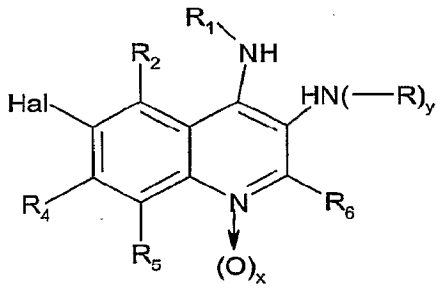
x, y, X, R_1, R_2, R_4, R_5 and R_6 are as defined above; and

if desired, transforming an obtainable compound of formula (I) into a different compound of formula (I), transforming a salt of an obtainable compound of formula (I) into the free compound or a different salt, or an obtainable free compound of formula (I) into a salt; and/or separating an obtainable mixture of isomers of compounds of formula (I) into the individual isomers.

In the following, more detailed description of the preferred process conditions, x, y, R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, and R have the meanings given for compounds of the formula (I), if not indicated otherwise.

Starting Materials

A compound of formula (II) of the first preferred embodiment is prepared by reacting a compound of formula (IIa)



(IIa)

wherein

x, y, R_1, R_2, R_4, R_5 and R_6 are as mentioned for a compound of the formula (I); and

R is as defined below under a), b) or c), respectively,

a) for the manufacture of a compound of the formula (II), wherein X is C=O and the dashed line in formula (I) bonding X to N is absent, y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen, with an active derivative of a compound of the formula (III)

A-X-A (III)

wherein X is C=O and each A, independently of the other, is a carbonyl-activating group;

b) for the manufacture of a compound of the formula (II), wherein X is C=S and the dashed line in formula (I) bonding X to N is absent, y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen, with CS_2 or Cl-C(=S)-Cl; or

c) for the manufacture of a compound of the formula (II), wherein X is (CR_7) wherein R_7 is hydrogen or an organic or inorganic moiety with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, with an activated derivative of a compound of formula (IVa), (IVb) or (IVc) or a derivative of one of these compounds:

R_7-COOH (IVa)

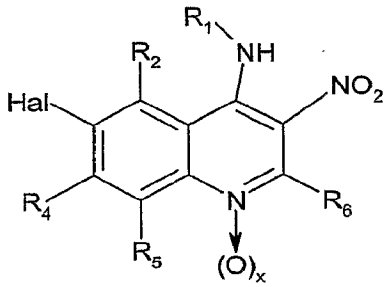
R_7-CN (IVb)

R_7-CHO (IVc)

wherein R_7 is hydrogen, an organic or inorganic moiety, especially C_1-C_7lower alkyl, amino or amino lower alkyl;

wherein functional groups which are present in the starting compounds in processes a) to c) and are not intended to take part in the reaction, are present in protected form if necessary, and protecting groups that are present are cleaved, wherein said starting compounds may also exist in the form of salts provided that a salt-forming group is present and a reaction in salt form is possible.

A compound of the formula (II), wherein R is hydrogen and y is 1 is preferably prepared by hydrogenation of a compound of the formula (V)



(V)

wherein the substituents and symbols are defined as for compounds of the formula (I) (x is preferably zero), in the presence of an appropriate catalyst, e.g. a skeleton based catalyst, such as Raney-Ni, with hydrogen in an appropriate solvent, e.g. an alcohol, such as methanol, at preferred temperatures between 0°C and 50°C, e.g. at room temperature.

The corresponding compounds of the formula (II), wherein R is an organic moiety that can be bound to nitrogen, especially a carbon-bound one, can be prepared by reaction of a compound of formula (II), wherein R is hydrogen and y is 1 (see preceding paragraph) with a compound of the formula (VI)

R—L **(VI)**

wherein R is an organic moiety bound to L via a carbon atom and L is a leaving group, especially halo, such as chloro, bromo or iodo, or arylsulfonyl, e.g. toluenesulfonyl, in an

appropriate solvent, preferably in the presence of a tertiary nitrogen base, such as pyridine or triethylamine.

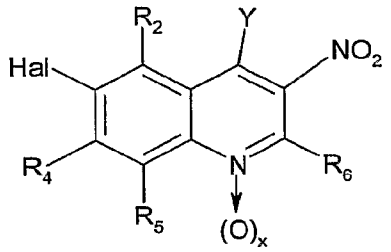
Alternatively, a compound of the formula (II), wherein R is hydrogen and y is 1 can be reacted with a carbonyl containing compound of the formula (VI*) or (VI**)

$$R^*—CHO \qquad \textbf{(VI*)}$$

$$R^*—CO—R^{**} \qquad \textbf{(VI**)}$$

wherein R* and R** are the same or different and each is as an organic moiety bound to the CO moiety via a carbon atom, followed by reduction of the resulting enamine with an appropriate reductant, e.g. a complex hydride, such as an alkalimetal cyanoborohydride, e.g. sodium-cyanoborohydride, e.g. in the same solvent and at temperatures between -10°C and 40°C, e.g. at 10°C, the total reaction summing up to reductive amination.

A compound of formula (V) is preferably prepared by reacting a compound of the formula (VII)



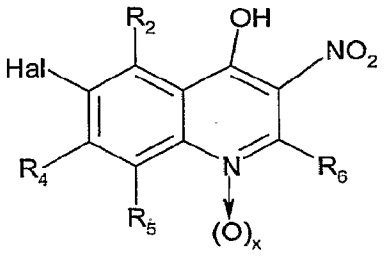
(VII)

wherein Y is halo, especially chloro, and the other moieties and symbols have the meanings indicated for compounds of the formula (I) (x is preferably zero), with a compound of the formula (VIII)

$$R_1—NH_2 \qquad \textbf{(VIII)}$$

wherein R_1 is as defined for a compound of the formula (I), in an appropriate solvent, preferably a lower alkylcarboxylic acid, such as acetic acid, at preferred temperatures between 10 C and reflux temperature of the reaction mixture, e.g. between 20°C and 140°C.

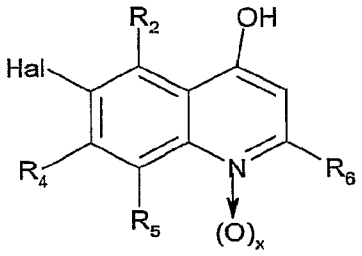
A compound of the formula (VII) can be prepared by reacting a compound of the formula (IX)



(IX)

wherein the moieties and symbols have the meanings indicated for a compound of the formula (I) (x is preferably zero), with an inorganic acid halogenide, especially $POCl_3$ (preferably without solvent) at elevated temperatures, e.g. between 100°C and 150°C or under reflux.

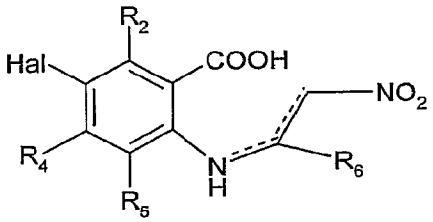
A compound of the formula (IX) is known in the art, can be synthesized according to methods known in the art and/or is commercially-available. For example, it can be synthesized by reacting a compound of the formula (X)



(X)

wherein the moieties and symbols have the meanings indicated for a compound of the formula (I) (x is preferably zero) with nitric acid (aqueous) at a preferred temperature between 50°C and 100°C, e.g. at 85°C.

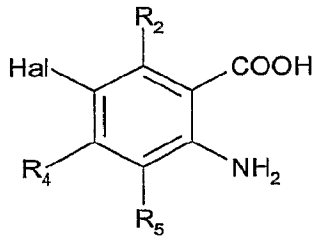
A compound of the formula (IX), can alternatively be synthesized by reacting a compound of the formula (XI)



(XI)

wherein the moieties and symbols have the meanings indicated for a compound of the formula (I), with an anhydride of a carbonic acid, especially acetic anhydride, preferably in the presence of an alkali metal salt of a carboxylic acid, e.g. potassium acetate, at a preferred temperature between 50°C and 150°C, e.g. at ca. 100-140°C.

A compound of the formula (XI) can be obtained, for example, by converting a compound of the formula (XII)



(XII)

to the corresponding compound of the formula (XI) by reacting nitromethane in the presence of an alkali metal hydroxide, especially sodium hydroxide, at preferred temperatures between approximately 0°C and 60°C, e.g. between 0°C and room temperature, then pouring the product under cooling to approximately 0°C into conc. HCl and adding the compound of the formula (XII) and further conc. HCl, subsequently allowing for further reaction at preferred temperatures between 0°C and room temperature to result in the corresponding compound of formula (XI).

Other starting materials are either known in the art, can be prepared according to methods that are known in the art, e.g. in analogy to the methods described hereinabove or in the examples, and/or are commercially-available.

The present invention relates also to novel starting materials and/or intermediates and to processes for their preparation. The starting materials used and the reaction conditions selected are preferably those that result in the compounds described as being preferred.

Detailed Description of Preferred Reaction Conditions

The reaction described under (a) preferably takes place under conditions known in the art, especially in an appropriate solvent, such as a halo-lower alkane, e.g. dichloromethane, or a lower alkylnitrile, such as acetonitrile, and under elevated temperatures, preferably in the range from 40°C to the reflux temperature of the reaction mixture, especially under reflux. In the compound of the formula (III), each A is, independently of the other, preferably halo, trichloromethyl, succinimido or 1-imidazolo. For example, if the compound of the formula (III) is trichloromethyl chloroformate, the reaction preferably takes place under anhydrous conditions in an appropriate aprotic solvent, e.g. a halogenated hydrocarbon, such as dichloromethane, at preferred temperatures between 0°C and 50°C, e.g. at room temperature.

The reaction described under (b) with CS_2 or Cl-C(=S)-Cl preferably takes place in the presence of a base, especially a tertiary amine, such as tri-lower alkylamine, preferably triethylamine, or pyridine, an alkalimetal carbonate or -bicarbonate, e.g. sodium bicarbonate, or a metal hydroxide, especially an alkali metal hydroxide, such as sodium- or potassium hydroxide, in a polar organic solvent, especially an alcohol, at temperatures between 10°C and the reflux temperature, more preferably between 20°C and 100°C.

The reaction described under (c) preferably takes place in the presence of an active derivative of a compound of the formula (IVa), (IVb) and (IVc) as solvent or other appropriate solvents or solvent mixtures at preferred temperatures between 30°C and the reflux temperature of the reaction mixture, more preferably under reflux. An activated derivative of a compound of the formula (IVa) is especially a tri-lower alkyl orthoester of the carbonic acid of formula (IVa), especially a tri-ethyl derivative, such as triethylorthoformate or a tetramethyl derivative, such as tetramethyl orthocarbonate. Alternatively, the respective reactive derivative of an acid of the formula (IVa) is formed *in situ*, e.g. in the presence of polyphosphoric acid (also as solvent) at elevated temperatures, e.g. between 100°C and 140°C. An activated derivative of a compound of formula (IVb) is especially a halo derivative, such as cyanogen bromide.

Compounds of formula (I) can be transformed into different compounds of formula (I).

Especially, the following transformations are of interest:

In compounds of the formula (I), wherein R_1 carries a cyano or cyano-lower alkyl substituent, this substituent can be converted into an aminomethyl or aminomethyl-lower alkyl group, respectively, by hydrogenation, e.g. with hydrogen in the presence of an appropriate catalyst, such as a Raney catalyst, especially Raney-Ni, in an appropriate solvent, such as an alcohol, especially methanol or ethanol, or a cyclic ether, such as tetrahydrofuran, or a mixture thereof, in the presence of ammonia, preferably at temperatures between 0°C and 50°C, e.g. at room temperature.

In compounds of the formula (I), wherein R_1 carries a cyano or cyano-lower alkyl substituent or R_7 is any one of these substituents, this substituent can be converted into a *N*-hydroxyamidino or *N*-hydroxyamidino-lower alkyl group, respectively, by reaction with a hydroxylamine salt of an organic or inorganic acid, e.g. a hydroxylamine halogenide, in a

polar solvent, e.g. a di-lower alkyl lower alkanoylamide, especially dimethyl formamide, in the presence of water at preferred temperatures between 10°C and 100°C, e.g. at 20-75°C, in the presence of a base, especially an alkali metal carbonate, such as sodium carbonate.

In compounds of the formula (I), wherein R_1 is 2-haloaryl, e.g. 2-chlorophenyl, the halogen can be removed by hydrogenation with hydrogen in an appropriate solvent, e.g. in an alcohol, such as methanol, or a *N,N*-di-lower alkyl-loweralkanoylamide, such as dimethylformamide, or a mixture thereof, and a catalyst, such as a noble metal on a carrier material, e.g. palladium on charcoal (Pd-C), at preferred temperatures between 0°C and 50°C, e.g. at room temperature, to the corresponding compound wherein R_1 is aryl, e.g. phenyl.

In a compound of the formula (I), wherein a hydroxyamidino substituent is present (e.g. as mentioned in the last paragraph), this substituent can be converted into the corresponding amidino substituent by hydrogenation in the presence of an acid, such as hydrochloric acid, and a catalyst, preferably a Raney metal catalyst, such as Raney-Ni, preferably at elevated temperatures, e.g. between 30°C and 70°C, e.g. at 50°C.

Compounds of the formula (I), wherein x and y or one of them are zero can be converted into the corresponding *N*-oxide compounds (x, y or both = 1, R = $\rightarrow$O) by oxidation in the presence of a peroxide, especially a peroxybenzoic acid derivative, such as 3-chloroperoxybenzoic acid, in the presence of a base, e.g. an alkali metal carbonate, such as sodium carbonate, and in an appropriate solvent, e.g. a halogenated hydrocarbon, such as chloroform or dichloromethane.

Compound of formula (I), where X is CR_7 and R_7 is NH_2 is prepared from the corresponding di-amino compound and cyanogen bromide in an appropriate solvent, e.g. ethanol, at temperatures between 0°C and 50°C, e.g. room temperature.

A compound of formula (I), where X is CR_7 and R_7 is OCH_3 is prepared from the corresponding di-amino compound and tetramethyl orthocarbonate in the presence of an appropriate solvent, e.g. acetic acid, at elevated temperatures, e.g. 75°C.

A compound of formula (I), where X is CR_7 and R_7 is CF_3 is prepared from the di-amino compound and trifluoroacetic acid in the presence of an appropriate solvent, e.g. 4 N HCl, at elevated temperatures, e.g. 100°C.

A compound of formula (I) where X is CR_7 and R_7 is CH_3 is prepared from the corresponding di-amino compound and triethylorthoacetate at elevated temperatures, e.g. 130°C.

A compound of formula (I), where X is CR_7 and R_7 is lower alkyl is prepared from the corresponding di-amino compound and the corresponding aldehyde using catalytic amounts of acetic acid in an appropriate solvent, e.g. DCM, at temperatures between 0°C and 50°C, e.g. room temperature.

A compound of formula (I), where G is an alkenylene is prepared from the corresponding halo-derivative by reaction with a boronic acid, e.g. *trans*-phenylethenyl-boronic acid, in the presence of a catalyst, e.g. *bis*(triphenylphosphine)palladium(II) dichloride in potassium carbonate in DMF at elevated temperatures, 100°C, and under an inert atmosphere, e.g. an argon atmosphere.

A compound of formula (I), where G is and alkynylene is prepared by Sonogashira coupling. See Sonogashira et al, *Tetrahedron Lett*, p. 44671 (1975). The corresponding halo-derivative is reacted with the corresponding acetylene, e.g. phenylacetylene, in the presence of CuI, *bis*(benzonitrile)palladium (II) dichloride, tri-*tert*-butylphosphine, and diisopropylamine in dioxane, in an inert atmosphere, e.g. argon atmosphere.

A compound of the formula (I), wherein x is 1 and R_6 is hydrogen can be transformed into the corresponding compound wherein x is zero an R_6 is halo by reaction with an inorganic halogenide, e.g. $POCl_3$, in an appropriate solvent, e.g. a mixture of a di-lower alkyl alkanoylamide, such as dimethylformamide, and an aromatic hydrocarbon, e.g. toluene, at elevated temperatures, e.g. between 50°C and 90°C.

A compound of the formula (I), wherein R_6 is halo can be converted into a compound of the formula (I), wherein R_6 is amino substituted by one or two moieties selected from the group consisting of lower alkyl, substituted lower alkyl moieties, aryl, cycloalkyl and mercapto-lower alkyl by reaction with the corresponding primary or secondary amine, respectively, in an appropriate solvent, e.g. an alcohol, especially methanol or 2-ethoxyethanol, at temperatures between 100°C and 130°C (if necessary in a sealed reaction vessel, e.g. a sealed tube).

A compound of the formula (I), wherein X is (CR_7) and R_7 is halogen can be obtained from the corresponding compound wherein R_7 is hydrogen by reaction with the corresponding halogen succinimide, especially *N*-bromosuccinimide, in the presence of the corresponding iron(III)halogenide, especially $FeBr_3$, in the absence or presence of an appropriate solvent at elevated temperatures, preferably under reflux.

A compound of the formula (I), wherein X is (CR_7) and R_7 is cyano can be obtained from the corresponding compound wherein R_7 is $-CONH_2$ by reaction with an inorganic acid halogenide, especially $POCl_3$, in an appropriate base, especially pyridine, preferably at elevated temperatures, more preferably between 25°C and 80°C. Alternatively, the compound can be obtained from a compound of the formula (I), wherein R_7 is bromo (as obtainable in the last paragraph) by reaction in the presence of CuCN and a catalyst, especially), *tris*(dibenzylideneacetone)dipalladium chloroform adduct and 1,1'-*bis*(diphenylphosphino)ferrocene, and of tetraethylammonium cyanide in an appropriate solvent, e.g. a cyclic ether, such as dioxane, at preferred temperatures (if necessary in a sealed tube) between 100°C and 150°C, e.g. at 140°C.

A compound of the formula (I), wherein X is C=O, y is 1 and R is unsubstituted or substituted alkyl, especially lower alkyl, can be obtained by converting the corresponding compound of the formula (I), wherein R is H with a halogenide, especially iodide, such as lower alkyl iodide, in the presence of a strong base, especially an alkali metal hydride, e.g. sodium hydride, in an appropriate aprotic solvent, e.g. a *N,N*-di-lower alkyl-lower alkanoylamide, at preferred temperatures in the range from 0-50°C, e.g. at room temperature, into said compound.

A compound of the formula (I), wherein X is C=O, y is 1 and R is aryl, especially phenyl, can be obtained by converting the corresponding compound of the formula (I), wherein R is H with an arylboronic acid, especially phenylboronic acid, in the presence of anhydrous cupric acetate and a tertiary amine, e.g. a tri-lower alkylamine, such as triethylamine, in an appropriate aprotic solvent, especially a halogenated hydrocarbon, such as dichloromethylene, at preferred temperatures between 0°C and 50°C, e.g. at room temperature, into said compound.

Salts of compounds of formula (I) having at least one salt-forming group may be prepared in a manner known *per se*. For example, salts of compounds of formula (I) having acid groups

may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g. the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of formula (I) are obtained in customary manner, e.g. by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of formula (I) containing acid and basic salt-forming groups, e.g. a free carboxy group and a free amino group, may be formed, e.g. by the neutralization of salts, such as acid addition salts, to the isoelectric point, e.g. with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known *per se* into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallization and/or chromatographic separation, for example over silica gel or by e.g. medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallization, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, e.g. using chromatographic methods, distribution methods, (re-)crystallization and the like.

Additional Process Steps

In the additional process steps, carried out as desired, functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or

may be protected for example by one or more protecting groups. The protecting groups are then wholly or partly removed according to one of the known methods.

Protecting groups, and the manner in which they are introduced and removed are described, for example, in "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973, and in "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Vol. 15/1, Georg-Thieme-Verlag, Stuttgart 1974 and in Theodora W. Greene, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York 1981. A characteristic of protecting groups is that they can be removed readily, i.e. without the occurrence of undesired secondary reactions, for example, by solvolysis, reduction, photolysis, acidolysis or alternatively under physiological conditions.

The end products of formula (I) may however also contain substituents that can also be used as protecting groups in starting materials for the preparation of other end products of formula (I). Thus, within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of formula (I) is designated a "protecting group", unless the context indicates otherwise.

General process conditions

The following applies in general to all processes mentioned hereinbefore and hereinafter, while reaction conditions specifically mentioned above or below are preferred:

All the above-mentioned process steps can be carried out under reaction conditions that are known *per se*, preferably those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, preferably solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example, ion exchangers, such as cation exchangers, e.g. in the H^+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example, in a temperature range of from about -100°C to about 190°C, preferably from approximately -80°C to approximately 150°C, for example, at from -80 to -60°C, at room temperature, at from -20 to 40°C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example, under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example, diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example, racemates or mixtures of diastereoisomers, for example, analogously to the methods described under "additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example, diethyl ether, or cyclic ethers, for example, tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as dichloromethane or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further *in situ*. In the process of the present invention those starting materials are preferably used which result in new compounds of formula (I) described at the beginning as being especially valuable. Special preference is given to reaction conditions that are analogous to those mentioned in the examples.

Pharmaceutical compositions

The invention relates also to pharmaceutical compositions comprising a compound of formula (I), to their use in the therapeutic (in a broader aspect of the invention also prophylactic) treatment or a method of treatment of a protein kinase dependent disease, especially the preferred diseases mentioned above, to the compounds for said use and to the preparation of pharmaceutical preparations, especially for said uses.

The present invention also relates to pro-drugs of a compound of formula (I) that convert *in vivo* to the compound of formula (I) as such. Any reference to a compound of formula (I) is therefore to be understood as referring also to the corresponding pro-drugs of the compound of formula (I), as appropriate and expedient.

The pharmacologically acceptable compounds of the present invention may be used, for example, for the preparation of pharmaceutical compositions that comprise an effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, as active ingredient together or in admixture with a significant amount of one or more inorganic or organic, solid or liquid, pharmaceutically acceptable carriers.

The invention relates also to a pharmaceutical composition that is suitable for administration to a warm-blooded animal, especially a human (or to cells or cell lines derived from a warm-blooded animal, especially a human, e.g. lymphocytes), for the treatment or, in a broader aspect of the invention, prevention of (= prophylaxis against) a disease that responds to inhibition of protein kinase activity, comprising an amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which is effective for said inhibition, especially the in, together with at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention are those for enteral, such as nasal, rectal or oral, or parenteral, such as intramuscular or intravenous, administration to warm-blooded animals (especially a human), that comprise an effective dose of the pharmacologically active ingredient, alone or together with a significant amount of a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, the body weight, the age and the individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

The invention relates also to a method of treatment for a disease that responds to inhibition of a protein kinase; which comprises administering an (against the mentioned disease) prophylactically or especially therapeutically effective amount of a compound of formula (I) according to the invention, especially to a warm-blooded animal, for example a human, that, on account of one of the mentioned diseases, requires such treatment.

The dose of a compound of the formula (I) or a pharmaceutically acceptable salt thereof to be administered to warm-blooded animals, for example humans of approximately 70 kg body weight, is preferably from approximately 3mg to approximately 10 g, more preferably from approximately 10 mg to approximately 1.5 g, most preferably from about 100 mg to about 1000 mg/person/day, divided preferably into 1-3 single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

The pharmaceutical compositions of the present invention are prepared in a manner known *per se*, for example by means of conventional dissolving, lyophilizing, mixing, granulating or confectioning processes.

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilized compositions that comprise the active ingredient alone or together with a carrier, for example mannitol, for such solutions or suspensions to be produced prior to use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting and/or emulsifying agents, solubilizers, salts for regulating the osmotic pressure and/or buffers, and are prepared in a manner known *per se*, for example by means of conventional dissolving or lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid

fatty acid esters that contain as the acid component a long-chained fatty acid having from 8-22, especially from 12-22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brasidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-*tert*-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6 carbon atoms and is a mono- or poly-hydroxy, for example a mono-, di- or tri-hydroxy, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. The following examples of fatty acid esters are therefore to be mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol trioleate, Gattefossé, Paris), "Miglyol 812" (triglyceride of saturated fatty acids with a chain length of C_8-C_{12}, Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The injection compositions are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into ampoules or vials and sealing the containers.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragée cores or capsules. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes using for example corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, and/or carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally

enteric, coatings, there being used, *inter alia*, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as ethylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Capsules are dry-filled capsules made of gelatin and soft sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired with stabilizers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable oily excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilizers and/or antibacterial agents to be added. Dyes or pigments may be added to the tablets or dragée coatings or the capsule casings, for example for identification purposes or to indicate different doses of active ingredient.

Combinations

A compound of the formula (I) may also be used to advantage in combination with other antiproliferative agents. Such antiproliferative agents include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active agents; alkylating agents; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; agents used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors; temozolomide (TEMODAL®); and leucovorin.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially

aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark LENTARON. Fadrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA or FEMAR. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g. under the trademark ORIMETEN. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g. breast tumors.

The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered, e.g., in the form as it is marketed, e.g. under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g. under the trademark EVISTA. Fulvestrant can be formulated as disclosed in US 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g. under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g. as disclosed in US 4,636,505.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in US 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g. under the trademark ZOLADEX. Abarelix can be formulated, e.g. as disclosed in US 5,843,901.

The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/ 17804). Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark

CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g. under the trademark HYCAMTIN.

The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, e.g. CAELYX), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark ETOPOPHOS. Teniposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark VM 26-BRISTOL. Doxorubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark FARMORUBICIN. Idarubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g. in the form as it is marketed, e.g. under the trademark NOVANTRON.

The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing agents and microtublin polymerization inhibitors including, but not limited to taxanes, e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochicine and epothilones and derivatives thereof, e.g. epothilone B or D or derivatives thereof. Paclitaxel may be administered e.g. in the form as it is marketed, e.g. TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g. under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark VINBLASTIN R.P.. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in US 5,010,099. Also included are Epothilone derivatives which are disclosed in WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are Epothilone A and/or B.

The term "alkylating agent" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark CYCLOSTIN. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark HOLOXAN.

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds disclosed in WO 02/22577, especially N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes Suberoylanilide hydroxamic acid (SAHA).

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-Fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating agents, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark GEMZAR. Also included is the monoclonal antibody trastuzumab which can be administered, e.g., in the form as it is marketed, e.g. under the trademark HERCEPTIN.

The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ELOXATIN.

The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, SU101, SU6668 and GFB-111;

b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I(IGF-IR), such as compounds which target, decrease or inhibit the

activity of IGF-IR, especially compounds which inhibit the IGF-IR receptor, such as those compounds disclosed in WO 02/092599;

d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family;

e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase;

h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g., imatinib;

i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family and their gene-fusion products (e.g. BCR-Abl kinase), such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib; PD180970; AG957; NSC 680410; or PD173955 from ParkeDavis;

j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK and Ras/MAPK family members, or PI(3) kinase family, or of the PI(3)-kinase-related kinase family, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in US 5,093,330, e.g. midostaurin; examples of further compounds include e.g. UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds such as those disclosed in WO 00/09495; FTIs; PD184352 or QAN697 (a P13K inhibitor);

k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin.

A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin);

l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers), such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180); e.g. trastuzumab (HERCEPTIN), cetuximab, Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are disclosed in WO 03/013541; and

m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor.

Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, PTEN or CDC25, e.g. okadaic acid or a derivative thereof.

Compounds which induce cell differentiation processes are e.g. retinoic acid, α- γ- or δ-tocopherol or α- γ- or δ-tocotrienol.

The term cyclooxygenase inhibitor as used herein includes, but is not limited to, e.g. Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark SKELID. "Pamidronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZOMETA.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.

The term " biological response modifier" as used herein refers to a lymphokine or interferons, e.g. interferon γ.

The term "inhibitor of Ras oncogenic isoforms", e.g. H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras e.g. a "farnesyl transferase inhibitor" e.g. L-744832, DK8G557 or R115777 (Zarnestra).

The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g. telomestatin.

The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are e.g. bengamide or a derivative thereof.

The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include e.g. PS-341 and MLN 341.

The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

The term "agents used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors e.g. compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors e.g. compounds which target, decrease or inhibit anaplastic lymphoma kinase.

Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g. PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of

HSP90 e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erlotinib (Tarceva™), bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant e.g. intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

For the treatment of acute myeloid leukemia (AML), compounds of formula (I) can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula (I) can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

The term "antileukemic compounds" includes, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate.

Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065, in particular, *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof and *N*-hydroxy-3-[4-[(2-hydroxyethyl){2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt.

Compounds which target, decrease or inhibit the activity of serine/theronine mTOR kinase are especially compounds, proteins or antibodies which inhibit members of the mTOR kinase family e.g. RAD, RAD001, CCI-779, ABT578, SAR543, rapamycin and derivatives thereof; AP23573 from Ariad; everolimus (CERTICAN); and sirolimus.

Somatostatin receptor antagonists as used herein refers to agents which target, treat or inhibit the somatostatin receptor such as octreoride, and SOM230.

Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in *Principles and Practice of Oncology*, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

The term EDG binders as used herein refers a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

CERTICAN (everolimus, RAD) an investigational novel proliferation signal inhibitor that prevents proliferation of T-cells and vascular smooth muscle cells.

The term ribonucleotide reductase inhibitors refers to pyrimidine or puring nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1*H*-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8 mentioned in Nandy et al., *Acta Oncologica*, Vol. 33, No. 8, pp. 953-961 (1994).

The term "*S*-adenosylmethionine decarboxylase inhibitors" as used herein includes, but is not limited to the compounds disclosed in US 5,461,076.

Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by Prewett et al, *Cancer Res*, Vol. 59, pp. 5209-5218 (1999); Yuan et al., *Proc Natl Acad Sci U S A*, Vol. 93, pp. 14765-14770 (1996); Zhu et al., *Cancer Res*, Vol. 58, pp. 3209-3214 (1998); and Mordenti et al., *Toxicol Pathol*, Vol. 27, No. 1, pp. 14-21 (1999); in WO 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., *Cell*, Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described by O'Reilly et al., *Cell*, Vol. 88,

pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. rhuMAb and RHUFab, VEGF aptamer e.g. Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Avastan.

Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing agents to treat or prevent cancers. Examples of photodynamic therapy includes treatment with agents, such as e.g. VISUDYNE and porfimer sodium.

Angiostatic steroids as used herein refers to agents which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone. hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

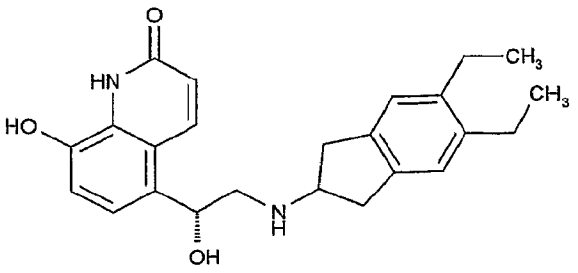
Implants containing corticosteroids refers to agents, such as e.g. fluocinolone, dexamethasone.

Other chemotherapeutic agents include, but are not limited to, plant alkaloids, hormonal agents and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; or miscellaneous agents or agents with other or unknown mechanism of action.

The compounds of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. A compound of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Accordingly the invention includes a combination of a compound of the invention as hereinbefore described with an anti-inflammatory, bronchodilatory, antihistamine or anti-tussive drug substance, said compound of the invention and said drug substance being in the same or different pharmaceutical composition.

Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/035668, WO 03/048181, WO 03/062259, WO 03/064445, WO 03/072592, non-steroidal glucocorticoid receptor agonists such as those described in WO 00/00531, WO 02/10143, WO 03/082280, WO 03/082787, WO 03/104195, WO 04/005229;

LTB4 antagonists such LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247 and those described in US 5451700; LTD4 antagonists such as montelukast and zafirlukast; PDE4 inhibitors such cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; A2a agonists such as those disclosed in EP 409595A2, EP 1052264, EP 1241176, WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/039762, WO 04/039766, WO 04/045618 and WO 04/046083; A2b antagonists such as those described in WO 02/42298; and beta-2 adrenoceptor agonists such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of WO 0075114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula I of WO 04/16601, and also compounds of WO 04/033412.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate, but also those described in WO 01/04118, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/87094, WO 04/05285, WO 02/00652, WO 03/53966, EP 424021, US 5171744, US 3714357, WO 03/33495 and WO 04/018422.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine as well as those disclosed in WO 03/099807, WO 04/026841 and JP 2004107299.

Other useful combinations of compounds of the invention with anti-inflammatory drugs are those with antagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-amin-ium chloride (TAK-770), and CCR-5 antagonists described in US 6166037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

The above-mentioned compounds, which can be used in combination with a compound of the formula (I), can be prepared and administered as described in the art, such as in the documents cited above.

A compound of the formula (I) may also be used to advantage in combination with known therapeutic processes, for example, the administration of hormones or especially radiation. A compound of formula (I) may in particular be used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

By "combination", there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the formula (I) and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g. synergistic, effect, or any combination thereof.

EXAMPLES

The following examples serve to illustrate the invention without limiting the scope thereof:

Abbreviations

Boc	*tert*-butoxycarbonyl
conc.	concentrated
DMF	*N,N*-dimethylformamide
EtOAc	ethyl acetate
ES-MS	electrospray mass spectrometry
Grad	gradient
HPLC	high-pressure liquid chromatography
mL	mililitre(s)
m.p.	melting point
MS	mass spectrum
Prep. HPLC	preparative HPLC reverse phase C_{18}
sat.	saturated
RT	room temperature
t_{ret}	HPLC retention time in minutes
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Where no temperature values are given, the reaction takes place at ambient (room) temperature.

Ratios of solvents (e.g. in eluents or solvent mixtures) are given in volume by volume ($^{v}/_{v}$).

HPLC linear gradient between A = H_2O/TFA 1000:1 and B = acetonitrile/TFA 1000:1

Grad 1: 20-100% B in 5 minutes and 1.5 minutes at 100% B, column: Nucleosil 100-3 C_{18} reverse phase, 70 mm x 4 mm, particle size 3 µm, Å (Macherey & Nagel, Düren, Germany); flow rate: 1.25 ml/min.; detection at 215 nM.

Grad 2: 2-100% B in 4.5 minutes and 1 minute at 100% B, column: Chromolith Performance 100 mm x 4.5 mm (Merck, Darmstadt, Germany); flow rate 2 mL/min.; detection at 215 nM.

Grad 3: 2-100% B in 7 minutes and 3 minutes at 100% B; column: Nucleosil C_{18} reverse phase; 250 mm x 4.6 mm (SMT, Burkard Instruments, Dietikon, Switzerland); particle size 5 µm, 100 Å; flow rate: 2.0 mL/min.; detection at 215 nm.

Example 1

2-[4-(8-Phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine

74 mg (0.151 mmol) of {2-[4-(8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (Example **1h**) are dissolved in 2 mL of TFA-H_2O (19:1 or 1:1) and the progress of the reaction is monitored by analytical HPLC. After complete removal of the Boc protecting group, the solvent is evaporated to dryness and the residue purified by prep. HPLC. The pure fractions are condensed, basified with $NaHCO_3$ and extracted with ethyl acetate (3 x). The organic layers are dried over $MgSO_4$, filtered and evaporated to dryness to give 2-[4-(8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine as an off-white solid: ES-MS: 389 $(M+H)^+$; analytical HPLC: t_{ret}= 2.98 minutes (Grad 1).

Example 1a

5-Bromo-2-(2-nitro-vinylamino)-benzoic acid

A suspension of 25 g (16 mmol) of 2-amino-5-bromo-benzoic acid (Fluka, Buchs, Switzerland) in H_2O-HCl (37%) (10:1) is stirred for 8 hours and then filtered (Solution **A**).

8.17 g (255 mmol) of nitromethane (Fluka, Buchs, Switzerland) are added over 10 minutes to an ice-bath cooled mixture of 35 g of ice and 15.3 g (382 mmol) of NaOH. After stirring for 1 hour at 0°C and 1 hour at RT, the solution is added at 0°C to 28 g of ice and 42 mL of HCl (37%) (Solution **B**). Solutions **A** and **B** are combined and the reaction mixture is stirred for 18 hours at RT. The yellow precipitate is filtered off and washed with H_2O. 5-Bromo-2-(2-nitro-vinylamino)-benzoic acid is dried *in vacuo* at 40°C. ES-MS: 287, 289 $(M+H)^+$, Br pattern.

^{1}H NMR (DMSO-d_6): δ 13.7-14.6 (br, s, 1H), 12.94 (d, 1H), 8.07 (d, 1H), 8.03 (dd, 1H), 7.83 (dd, 1H), 7.71 (d, 1H), 6.76 (d, 1H); analytical HPLC: t_{ret}= 3.93 minutes (Grad 1).

Example 1b

6-Bromo-3-nitro-quinolin-4-ol

29 g (101 mmol) of 5-bromo-2-(2-nitro-vinylamino)-benzoic acid (Example **1a**) and 11.9 g (121 mmol) of potassium acetate in 129 mL (152 mmol) of acetic anhydride are stirred for 1.5 hours at 120°C. The precipitate is filtered-off and washed with acetic acid until the filtrate is colorless and then with H_2O. 6-Bromo-3-nitro-quinolin-4-ol is dried *in vacuo*. ES-MS: 269, 271 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.01 minutes (Grad 1).

Example 1c

6-Bromo-4-chloro-3-nitro-quinoline

7.8 g (29 mmol) of 6-bromo-3-nitro-quinolin-4-ol (Example **1b**) in 58 mL (230 mmol) of $POCl_3$ are stirred for 2 hours at 120°C. The mixture is cooled to rt and poured slowly into ice-water. The precipitate is filtered-off, washed with ice-cold water, and dissolved in CH_2Cl_2. The organic phase is washed with cold brine, and the aqueous phase is discarded. After drying over $MgSO_4$, the organic solvent is evaporated to dryness to provide 6-bromo-4-chloro-3-nitro-quinoline.

^{1}H NMR ($CDCl_3$): δ 9.20 (s, 1H), 8.54 (d, 1H), 8.04 (d, 1H), 7.96 (dd, 1H); analytical HPLC: t_{ret}= 4.32 minutes (Grad 2).

Example 1d

[2-(4-Amino-phenyl)-ethyl]-carbamic acid *tert*-butyl ester

[2-(4-Amino-phenyl)-ethyl]-carbamic acid *tert*-butyl ester is obtained as described in *J Med Chem*, Vol. 35, p. 4264 (1992); ES-MS: 237 $(M+H)^+$; analytical HPLC: t_{ret}= 2.54 minutes (Grad 2).

Example 1e

{2-[4-(6-Bromo-3-nitro-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

0.66 g (2.31 mmol) of 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) and 0.60 g (2.54 mmol) of [2-(4-amino-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (Example **1d**) are dissolved in 7 mL of acetic acid and stirred for 1 hour. After this time, water is added and the yellow precipitate is filtered-off and washed with H_2O. The solid is dissolved in EtOAc-THF (3:1), washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The organic phase is evaporated to dryness to give {2-[4-(6-bromo-3-nitro-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester as a yellow solid. ES-MS: 487, 489 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.92 minutes (Grad 2).

Example 1f

{2-[4-(3-Amino-6-bromo-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

1.1 g (2.26 mmol) of {2-[4-(6-bromo-3-nitro-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (Example **1e**) is shacked in 26 mL of MeOH-THF (2:1) under 1.1 bar of H_2 in the presence of 0.5 g of Raney-Ni for 3 hours. After completion of the reaction, the catalyst is filtered-off and the filtrate is evaporated to dryness to give {2-[4-(3-amino-6-bromo-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester as a yellow foam. ES-MS: 457, 459 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.41 minutes (Grad 2).

Example 1g

{2-[4-(8-Bromo-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

1.03 g (2.26 mmol) of {2-[4-(3-amino-6-bromo-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester in 30 mL triethylorthoformate is heated for 2 hours at 105°C, and then evaporated *in vacuo* to dryness. The residue is purified by flash chromatography on silica gel (CH_2Cl_2-MeOH 3:197 to 1:24) to provide {2-[4-(8-bromo-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester as a pink foam. ES-MS: 467, 469 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.36 minutes (Grad 2).

Example 1h

{2-[4-(8-Phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester

To 80 mg (0.171 mmol) of {2-[4-(8-bromo-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (Example **1g**), 1 mg (0.0053 mmol) of CuI and 3 mg (0.0078 mmol) of *bis*(benzonitrile)palladium (II) chloride in 0.25 mL of dioxane under an argon atmosphere are added 21 mg (0.205 mmol) of phenylacetylene (Fluka, Buchs, Switzerland), 0.05 mL (0.012 mmol) of 0.25 M tri-*tert*-butylphosphine in dioxane and 20.3 mg (0.205 mmol) of diisopropylamine. The reaction mixture is stirred for 2 hours, and then quenched with aqueous sat. $NaHCO_3$ and extracted with EtOAc. The organic layer is washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue is purified by flash chromatography on silica gel (CH_2Cl_2-MeOH 99:1 to 193:7) to give {2-[4-(8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester as an oil. ES-MS: 489 $(M + H)^+$; analytical HPLC: t_{ret}= 4.76 minutes (Grad 1).

The following compounds (see Table 1) are prepared as described in Example **1** by reacting {2-[4-(8-bromo-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (Example **1g**), with the appropriate alkyne as shown in Example **1h**.

Example 2 3-methoxyphenylacetylene (Fluka, Buchs, Switzerland);

Example 3 4-methoxyphenylacetylene (Fluka, Bucks, Switzerland);

Example 4 3-ethynylpyridine (Aldrich, Buchs, Switzerland);

Example 5 5-ethynyl-2-methoxy-pyridine (Example **5a**);

Example 6 5-ethynyl-benzo[1,3]dioxole (Example **6a**); and

Example 7 4-ethynyl-benzenesulfonamide (Example **7a**).

Table 1

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
2	2-{4-[8-(3-Methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	419	3.07 Grad 1
3	2-{4-[8-(4-Methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	419	3.01 Grad 1
4	2-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	390	1.95 Grad 1
5	2-{4-[8-(6-Methoxy-pyridin-3-ylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	420	2.60 Grad 2
6	2-[4-(8-Benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	433	3.01 Grad 1
7	4-{1-[4-(2-Amino-ethyl)-phenyl]-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide	468	2.54 Grad 1

Example 5a

5-Ethynyl-2-methoxy-pyridine

To a cold solution of 2.2 g (10.6 mmol) of 2-methoxy-5-trimethylsilanylethynyl-pyridine (Example **5b**) in 25 mL of THF is slowly added a solution of 3.68 g (11.7 mmol) of tetrabutylammonium fluoride trihydrate in 5 mL of H_2O. The reaction mixture is stirred for 1 hour. After this time, the reaction mixture is treated with aqueous sat. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer is washed with aqueous sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica gel (hexane/EtOAc (20:1) to (10:1)) to give a brown oil. 5-Ethynyl-2-methoxy-pyridine is obtained by bulb to bulb distillation at reduced pressure as a colorless liquid. ES-MS: 134 $(M + H)^+$; analytical HPLC: t_{ret}= 3.39 minutes (Grad 2).

Example 5b

2-Methoxy-5-trimethylsilanylethynyl-pyridine

To 41 mg (0.213 mmol) of CuI and 122 mg (0.319 mmol) of *bis*(benzonitrile)palladium (II) chloride in 10 mL of dioxane are added under an argon atmosphere 2 g (10.6 mmol) of 5-bromo-2-methoxy-pyridine (Aldrich, Buchs, Switzerland), 1.25 g (12.8 mmol) of trimethylsilylacetylene (Fluka, Buchs, Switzerland), 2.55 mL (0.638 mmol) of 0.25 M tri-*tert*-butylphosphine in dioxane and 1.3 g (12.8 mmol) of diisopropylamine. The reaction mixture is stirred for 12 hours. After this time, the reaction mixture is treated with aqueous sat. $NaHCO_3$ and extracted with EtOAc. The organic layer is washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica gel (hexane-EtOAc (20:1) to (10:1)) to provide 2-Methoxy-5-trimethylsilanylethynyl-pyridine as a brown oil. ES-MS: 206 $(M + H)^+$; analytical HPLC: t_{ret}= 4.85 minutes (Grad 2).

Example 6a

5-Ethynyl-benzo[1,3]dioxole

5-Ethynyl-benzo[1,3]dioxole is obtained as described in Example **5a** using 5-bromo-benzo[1,3]-dioxole (Fluka, Buchs, Switzerland) instead of 5-bromo-2-methoxypyridine, analytical HPLC: t_{ret}= 3.71 minutes (Grad 2).

Example 7a

4-Ethynyl-benzenesulfonamide

4-Ethynyl-benzenesulfonamide is obtained as described in Example **5a** using 4-bromo-benzenesulfonamide (Fluka, Buchs, Switzerland) instead of 5-bromo-2-methoyxpyridine. ES-MS: 180 $(M-H)^+$; analytical HPLC: t_{ret}= 2.65 minutes (Grad 2).

The following compounds (see Table 2) are prepared as described in Example **1** using [3-(4-amino-phenyl)-propyl]-carbamic acid *tert*-butyl ester (Example **8a**) and the appropriate alkyne according to Example **1h**.

Example 8 **phenylacetylene (Fluka, Buchs, Switzerland);**

Example 9 **3-methoxyphenylacetylene (Fluka, Buchs, Switzerland);**

Example 10 **4-methoxyphenylacetylene (Fluka, Bucks, Switzerland);**

Example 11 **3-ethynylpyridine (Aldrich, Buchs, Switzerland);**

Example 12 **5-ethynyl-benzo[1,3]dioxole (Example 6a); and**

Example 13 **4-ethynyl-benzenesulfonamide (Example 7a).**

Table 2

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
8	3-[4-(8-Phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine	403	3.10 Grad 1
9	3-{4-[8-(3-Methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-propylamine	433	3.18 Grad 1
10	3-{4-[8-(4-Methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-propylamine	433	3.18 Grad 1
11	3-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine	404	2.27 Grad 1
12	3-[4-(8-Benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine	447	3.13 Grad 1
13	4-{1-[4-(3-Amino-propyl)-phenyl]-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide	482	2.66 Grad 1

Example 8a

[3-(4-Amino-phenyl)-propyl]-carbamic acid *tert*-butyl ester

2 g (11.4 mmol) of 3-(4-nitro-phenyl)-propionitrile (Example **8b**) and 0.5 g of Raney-Ni are shacked in 40 mL of THF-[MeOH/NH_3 (5%)] (1:1) under 1.1 bar of H_2 for 36 hours at 44°C. After completion of the reaction, the catalyst is filtered-off and the filtrate is evaporated *in vacuo*. The residue is dissolved in 20 mL of THF and 15 mL of aqueous sat. $NaHCO_3$. The solution is cooled with an ice-bath and 2.23 g (10.2 mmol) of $(Boc)_2O$ (Fluka, Buchs, Switzerland) in 10 mL of THF are added over 1 hour. The reaction mixture is stirred for 1.5 hours at RT, is diluted with water and extracted with EtOAc. The organic layer is washed with 10% of citric acid, sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and

evaporated. The residue is purified by flash chromatography on silica gel (hexane-EtOAc, 2:1 to 1:1) to provide [3-(4-amino-phenyl)-propyl]-carbamic acid *tert*-butyl ester as an oil. ES-MS: 251 $(M + H)^+$; analytical HPLC: t_{ret}= 2.85 minutes (Grad 1).

Example 8b

3-(4-Nitro-phenyl)-propionitrile

10.12 g (44 mmol) of 1-(2-bromo-ethyl)-4-nitro-benzene (Aldrich, Buchs, Switzerland) and 2.16 g (44 mmol) of NaCN in 110 mL of ethanol are refluxed for 16 hours. The reaction mixture is evaporated *in vacuo* and purified by flash chromatography on silica gel (CH_2Cl_2) to provide 3-(4-nitro-phenyl)-propionitrile as an off-white solid.

^{1}H NMR (DMSO-d_6): δ 8.23 (m, 2H), 7.62 (m, 2H), 3.06 (d, 2H), 2.92 (d, 1H); analytical HPLC: t_{ret}= 3.83 minutes (Grad 1).

The following compounds (see Table 3) are synthesized as described in Example 1 using 6-bromo-4,7-dichloro-3-nitro-quinoline in Example **1c**, which is obtained in analogy to 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) and starting from 2-amino-5-bromo-4-chloro-benzoic acid (Example **14a**) in Example **1a**, and the required alkyne in Example **1h**.

Example 14 phenylacetylene (Fluka, Buchs, Switzerland);

Example 15 3-methoxyphenylacetylene (Fluka, Buchs, Switzerland);

Example 16 4-methoxyphenylacetylene (Fluka, Bucks, Switzerland);

Example 17 3-ethynylpyridine (Aldrich, Buchs, Switzerland);

Example 18 5-ethynyl-benzo[1,3]dioxole (Example **6a**); and

Example 19 4-ethynyl-benzenesulfonamide (Example **7a**).

Table 3

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
14	2-[4-(7-Chloro-8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	423	3.55 Grad 1

15	2-{4-[7-Chloro-8-(3-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	453	3.62 Grad 1
16	2-{4-[7-Chloro-8-(4-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	453	3.59 Grad 1
17	2-[4-(7-Chloro-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	424	2.79 Grad 1
18	2-[4-(7-Chloro-8-benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	467	3.57 Grad 1
19	4-{1-[4-(2-Amino-ethyl)-phenyl]-7-chloro-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide	502	3.06 Grad1

Example 14a

2-Amino-5-bromo-4-chloro-benzoic acid

34.2 g (200 mmol) of 2-amino-4-chlorobenzoic acid (Fluka, Buchs, Switzerland) are dissolved in 1900 mL of methanol and the solution is cooled at -70°C. To this stirred solution, 11.2 mL (218 mmol) of bromine dissolved in 110 mL of methanol are added slowly. After 3 hours, the solution is added to ice-water and the aqueous phase is extracted with ether. The combined organic portions are washed with water, brine, dried over $MgSO_4$ and concentrated *in vacuo* to provide 2-amino-5-bromo-4-chloro-benzoic acid. 2-amino-5-bromo-4-chloro-benzoic acid, m.p. 228-230°C.

^{1}H NMR (DMSO-d_6): δ 7.85 (s, 1H), 6.95 (s, 1H).

The following compounds (see Table 4) are synthesized as described in Example 1 starting from 6-bromo-4,7-dichloro-3-nitro-quinoline in Example **1c**, [3-(4-amino-phenyl)-propyl]-carbamic acid *tert*-butyl ester (Example **8a**) in Example **1d** and the required alkyne in Example **1h**.

Example 20 phenylacetylene (Fluka, Buchs, Switzerland);

Example 21 3-methoxyphenylacetylene (Fluka, Buchs, Switzerland);

Example 22 4-methoxyphenylacetylene (Fluka, Bucks, Switzerland);

Example 23 3-ethynylpyridine (Aldrich, Buchs, Switzerland);

Example 24 5-ethynyl-benzo[1,3]dioxole (Example **6a**); and

Example 25 4-ethynyl-benzenesulfonamide (Example **7a**).

Table 4

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
20	3-[4-(7-Chloro-8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine	437	3.72 Grad 1
21	3-{4-[7-Chloro-8-(3-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-propylamine	467	3.80 Grad 1
22	3-{4-[7-Chloro-8-(4-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-propylamine	467	3.76 Grad 1
23	3-[4-(7-Chloro-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine	438	2.96 Grad 1
24	3-[4-(7-Chloro-8-benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine	481	3.72 Grad 1
25	4-{1-[4-(3-Amino-propyl)-phenyl]-7-chloro-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide	516	3.20 Grad 1

The following compounds (see Table 5) are synthesized as described in Example **1** using 6-bromo-4-chloro-7-fluoro-3-nitro-quinoline in Example **1c**, which is obtained in analogy to 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) and starting from 2-amino-5-bromo-4-fluoro-benzoic acid (Example **26a**) in Example **1a**, and the required alkyne in Example **1h**.

Example 26 phenylacetylene (Fluka, Buchs, Switzerland);

Example 27 3-methoxyphenylacetylene (Fluka, Buchs, Switzerland);

Example 28 4-methoxyphenylacetylene (Fluka, Bucks, Switzerland);

Example 29 3-ethynylpyridine (Aldrich, Buchs, Switzerland);

Example 30 5-ethynyl-benzo[1,3]dioxole (Example **6a**); and

Example 31 4-ethynyl-benzenesulfonamide (Example **7a**).

Table 5

Example	Compound name	ES-MS $(M + H)^+$	t_{ret} [min]
26	2-[4-(7-Fluoro-8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	407	3.24 Grad 1
27	2-{4-[7-Fluoro-8-(3-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	437	3.31 Grad 1
28	2-{4-[7-Fluoro-8-(4-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	437	3.29 Grad 1
29	2-[4-(7-Fluoro-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	408	2.46 Grad 1
30	2-[4-(7-Fluoro-8-benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	451	3.26 Grad 1
31	4-{1-[4-(2-Amino-ethyl)-phenyl]-7-fluoro-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide	486	2.81 Grad 1

Example 26a

2-Amino-5-bromo-4-fluoro-benzoic acid

2-Amino-5-bromo-4-fluoro-benzoic acid is obtained as described in Example **14a** starting with 2-amino-4-fluorobenzoic acid (Fluka, Buchs, Switzerland). 2-Amino-5-bromo-4-fluoro-benzoic acid; m.p. 216-218°C.

^{1}H NMR (DMSO-d_6): δ 7.85 (d, 1H), 6.64 (d, 1H).

The following compounds (see Table 6) are synthesized as described in Example **1** using triethyl orthoacetate (Fluka, Buchs, Switzerland), triethyl orthopropionate (Fluka, Buchs, Switzerland) or trimethyl orthobutyrate (Fluka, Buchs, Switzerland) in Example **1g**, and the required alkyne in Example **1h**.

Table 6

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
32	2-[4-(2-Methyl-8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	403	2.91 Grad 1
33	2-{4-[8-(3-Methoxy-phenylethynyl)-2-methyl-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	433	2.98 Grad 1
34	2-{4-[8-(4-Methoxy-phenylethynyl)-2-methyl-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine	433	2.99 Grad 1
35	2-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	404	1.90 Grad 1
36	2-[4-(2-Ethyl-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	418	2.22 Grad 2
37	2-[4-(3-Propyl-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	432	2.31 Grad 2

Example 38

3-[4-(8-*trans*-Styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine

71 mg (0.141 mmol) of {3-[4-(8-trans-styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propyl}-carbamic acid *tert*-butyl ester (Example **38b**) in 2 mL of TFA-H_2O (19:1) are stirred for 10 minutes. The solvent is evaporated to dryness and the residue purified by prep. HPLC. The pure fractions are condensed, basified with $NaHCO_3$ and extracted with ethyl acetate (3 x). The organic layers are dried over $MgSO_4$, filtered and evaporated to dryness to give 3-[4-(8-*trans*-styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine as an off-white solid; ES-MS: 405 $(M+H)^+$; analytical HPLC: t_{ret}= 3.00 minutes (Grad 1).

Example 38b

{3-[4-(8-*trans*-Styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propyl}-carbamic acid *tert*-butyl ester

70 mg (0.145 mmol) of {3-[4-(8-bromo-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propyl}-carbamic acid *tert*-butyl ester (intermediate for the synthesis of Example **8**), 32 mg (0.218 mmol) of *trans*-phenylethenylboronic acid (Aldrich, Buchs, Switzerland) and 6 mg (0.009 mmol) of *bis*(triphenylphosphino)palladium(II) chloride in 1.8 mL DMF and 0.364 mL (0.364 mmol) of 1 M aqueous potassium carbonate are stirred for 1 hour at 100°C under an

argon atmosphere. After this time, the reaction mixture is cooled down to RT and is treated with aqueous sat. $NaHCO_3$ and extracted with EtOAc (2 x). The combined organic layer are washed with brine (3 x), dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica gel (CH_2Cl_2-MeOH (99:1) to (193:7)) to give {3-[4-(8-*trans*-styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propyl}-carbamic acid *tert*-butyl ester as a solid. ES-MS: 505 $(M+H)^+$; analytical HPLC: t_{ret}= 4.71 minutes (Grad 1).

The following compounds (see Table 7) are synthesized as described in Example **38** starting from {3-[4-(8-bromo-7-chloro-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propyl}-carbamic acid *tert*-butyl ester (intermediate in the synthesis of Example **14**, i.e. the result of Step **1g** in Example **14**) or {2-[4-(8-bromo-7-chloro-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (intermediate in the synthesis of Example **20**, i.e. the result of Step **1g** in Example **20**).

Table 7

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
39	2-[4-(7-Chloro-8-styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine	425	3.32 Grad 1
40	3-[4-(7-Chloro-8-styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine	439	3.44 Grad 1

The following compounds (see Table 8) are prepared as described in Example **1** by reacting {2-[4-(8-bromo-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (Example **1g**), with the required alkyne as shown in Example **1h**.

Example 41 5-Ethynyl-2-fluoro-pyridine (Example **41a**);

Example 42 4-(5-Ethynyl-pyridin-2-yl)-morpholine (Example **42a**); and

Example 43 (5-Ethynyl-pyridin-2-yl)-dimethyl-amine (Example **43a**).

Table 8

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
41	2-{4-[8-(6-Fluoro-pyridin-3-ylethynyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-ethylamine	408	2.52 Grad 2

42	2-{4-[8-(6-Morpholin-4-yl-pyridin-3-ylethynyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-ethylamine	475	2.36 Grad 2
43	(5-{1-[4-(2-Amino-ethyl)-phenyl]-1H-imidazo[4,5-c]quinolin-8-ylethynyl}-pyridin-2-yl)-dimethyl-amine	433	2.17 Grad 2

Example 41a

5-Ethynyl-2-fluoro-pyridine

The title compound is obtained as described in Example **5a** using 5-bromo-2-fluoropyridine (Aldrich, Buchs, Switzerland) instead of 5-bromo-2-methoxypyridine. Analytical HPLC: t_{ret}= 3.03 minutes (Grad 2).

Example 42a

4-(5-Ethynyl-pyridin-2-yl)-morpholine

The title compound is obtained as described in Example **5a** using 4-(5-bromo-pyridin-2-yl)-morpholine (Example **42b**) instead of 5-bromo-2-methoxypyridine. ES-MS: 189 $(M+H)^+$; analytical HPLC: t_{ret}= 2.09 minutes (Grad 2).

Example 42b

4-(5-Bromo-pyridin-2-yl)-morpholine

3.0 g (12.7 mmol) of 2,5-dibromopyridine (Aldrich, Buchs, Switzerland) are suspended in 15.0 ml (172 mmol) of morpholine. The mixture is heated in a microwave for 100 min at 120 °C. After this time, 150 ml of ethylacetate are added and the solution is washed with 0.1 N hydrochloric acid, water, 0.1 N NaOH, and water. The organic phase is evaporated to dryness to provide the title compound; ES-MS: 243 $(M+H)^+$.

Example 43a

(5-Ethynyl-pyridin-2-yl)-dimethyl-amine

The title compound is obtained as described in Example **5a** using (5-bromo-pyridin-2-yl)-dimethyl-amine (Example **43b**) instead of 5-bromo-2-methoxypyridine. ES-MS: 147 $(M+H)^+$; analytical HPLC: t_{ret}= 1.90 minutes (Grad 2).

Example 43b

4-(5-Bromo-pyridin-2-yl)- dimethyl-amine

The title compound is obtained as described in Example **42b** using diethanolamine (Fluka, Buchs, CH) instead of morpholine. ES-MS: 201, 203 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 1.94 minutes (Grad 2).

Example 44

3-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propylamine

The title compound is obtained as described in Example **1** using [3-(4-amino-phenyl)-propyl]-carbamic acid tert-butyl ester (Example **8a**) as in Example **1e** and triethyl orthoacetate as described in Example **1g**. ES-MS: 418 $(M+H)^+$; analytical HPLC: t_{ret}= 2.28 minutes (Grad 2).

The following compounds (see Table 9) are synthesized as described in Example 1 with an alternative cyclisation of {2-[4-(3-amino-6-bromo-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (Example **1f**) using tetramethylothocarbonate (Aldrich, Buchs, Switzerland) (Example **45a**), cyclopropanecarboxaldehyde (Aldrich, Buchs, Switzerland) (Example **46a**) or isobuyraldehyde (Aldrich, Buchs, Switzerland) (Example **47a**).

Table 9

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
45	2-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethylamine	420	2.22 Grad 2
46	2-[4-(2-Cyclopropyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethylamine	430	2.31 Grad 2
47	2-[4-(2-Isopropyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethylamine	432	5.25 Grad 3

Example 45a

{2-[4-(8-Bromo-2-methoxy-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid tert-butyl ester

229 mg (0.5 mmol) of {2-[4-(3-amino-6-bromo-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (Example **1f**), 205 mg (1.5 mmol) of tetramethylorthocarbonate and 30 mg (0.5 mmol) of acetic acid are heated for 1 h at 75°C, and then quenched with aqueous sat. $NaHCO_3$ and extracted with EtOAc. The organic layer is washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue is purified by flash chromatography on silica gel (CH_2Cl_2-MeOH 98:2 to 96:4) to provide the title compound as an off-white foam. ES-MS: 497, 499 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.44 minutes (Grad 2).

Example 46a

{2-[4-(8-Bromo-2-cyclopropyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid tert-butyl ester

229 mg (0.5 mmol) of {2-[4-(3-amino-6-bromo-quinolin-4-ylamino)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (Example 1f), 88 mg (1.25 mmol) of cyclopropanecarboxaldehyde and 15 mg (0.25 mmol) of acetic acid in 5 ml CH_2Cl_2 are stirred for 44 h at RT, and then quenched with aqueous sat. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer is washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue is purified by flash chromatography on silica gel (CH_2Cl_2-MeOH 99:1 to 96:4) to provide the title compound as a yellow foam. ES-MS: 507, 509 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.56 minutes (Grad 2).

Example 47a

{2-[4-(8-Bromo-2-isopropyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-carbamic acid tert-butyl ester

The title compound is obtained as described in Example **46a** using isobutyraldehyde (Fluka, Buchs, Switzerland) instead of cyclopropanecarboxaldehyde. ES-MS: 510.9, 512.9 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 7.51 minutes (Grad 3).

The following compounds (see Table 10) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with the appropriate aniline as in Example **1e**.

Example 48 [2-(4-Amino-phenyl)-ethyl]-cyclopropyl-carbamic acid tert-butyl ester (Example **48a**);

Example 49 [2-(4-Amino-phenyl)-ethyl]-methyl-carbamic acid tert-butyl ester (Example **49a**);

Example 50 [1-(4-Amino-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (Example **50a**); and

Example 51 [1-(4-Amino-phenyl)-piperidin-4-ylmethyl]-carbamic acid tert-butyl ester (Example **51a**).

Table 10

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
48	Cyclopropyl-{2-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-amine	430	2.30 Grad 2
49	Methyl-{2-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-amine	404	2.20 Grad 2
50	1-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperidin-4-ylamine	445	2.32 Grad 2
51	C-{1-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperidin-4-yl}-methylamine	459	2.35 Grad 2

Example 48a

[2-(4-Amino-phenyl)-ethyl]-cyclopropyl-carbamic acid tert-butyl ester

2.13 g (6.91 mmol) of cyclopropyl-[2-(4-nitro-phenyl)-ethyl]-carbamic acid tert-butyl ester (Example **48b**) and 220 mg of Pd/C 10% are shacked in 60 ml of MeOH under 1.1 bar of H_2 for 1 h at RT. After completion of the reaction, the catalyst is filtered-off and the filtrate is evaporated *in vacuo* to give the title compound as an oil. ES-MS: 277 $(M+H)^+$; analytical HPLC: t_{ret}= 3.25 minutes (Grad 1).

Example 48b

Cyclopropyl-[2-(4-nitro-phenyl)-ethyl]-carbamic acid tert-butyl ester

To 1.8 g (8.73 mmol) of cyclopropyl-[2-(4-nitro-phenyl)-ethyl]-amine (Example **48c**) and 2.86 g (13.1 mmol) of $(Boc)_2O$ (Fluka, Buchs, Switzerland) in 17 ml of THF are added sat. aqueous $NaHCO_3$ (15 ml). The reaction mixture is stirred for 2 h at RT, then is extracted with EtOAc(2×). The organic layers are washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue is purified by flash chromatography on silica gel (hexane-EtOAc 8:1 to 7:1) to give the title compound as an oil. ES-MS: 307 $(M+H)^+$; analytical HPLC: t_{ret}= 5.44 minutes (Grad 1).

Example 48c

Cyclopropyl-[2-(4-nitro-phenyl)-ethyl]-amine

2.1 g (9.13 mmol) of 1-(2-bromo-ethyl)-4-nitro-benzene (Fluka, Buchs, CH) and 2.88 g (92.7 mmol) of cyclopropylamine (Fluka, Buchs, Switzerland) in 2 ml of acetonitrile are heated for 2 h at 45°C and then stirred 17 h at RT. The reaction mixture is quenched with 1 M aqueous K_2CO_3 and extracted with diethylether. The organic layer is dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the title compound as an oil. ES-MS: 207 $(M+H)^+$; analytical HPLC: t_{ret}= 2.40 minutes (Grad 1).

Example 49a

[2-(4-Amino-phenyl)-ethyl]-methyl-carbamic acid tert-butyl ester

The title compound is obtained as described in Example **48a** starting with methyl-[2-(4-nitro-phenyl)-ethyl]-carbamic acid tert-butyl ester (Example **49b**); ES-MS: 251 $(M+H)^+$; analytical HPLC: t_{ret}= 2.87 minutes (Grad 1).

Example 49b

Methyl-[2-(4-nitro-phenyl)-ethyl]-carbamic acid tert-butyl ester

The title compound is obtained as described in Example **48b** starting with methyl-[2-(4-nitro-phenyl)-ethyl]-amine (Example **49c**); ES-MS: 281 $(M+H)^+$; analytical HPLC: t_{ret}= 5.06 minutes (Grad 1).

Example 49c

Methyl-[2-(4-nitro-phenyl)-ethyl]-amine

The title compound is obtained as described in Example **48c** starting with 8 M methylamine in EtOH (Fluka, Buchs, CH); ES-MS: 181 $(M+H)^+$; analytical HPLC: t_{ret}= 1.89 minutes (Grad 1).

Example 50a

[1-(4-Amino-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester

The title compound is obtained as described in Example **48a** starting with [1-(4-nitro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester (Example **50b**); ES-MS: 292 $(M+H)^+$; analytical HPLC: t_{ret}= 2.41 minutes (Grad 2).

Example 50b

[1-(4-nitro-phenyl)-piperidin-4-yl]-carbamic acid tert-butyl ester

212 mg (1.5 mmol) of 4-fluoro-nitrobenzene (Aldrich, Buchs, Switzerland), 331 mg (1.65 mmol) of piperidin-4-yl-carbamic acid tert-butyl ester (Aldrich, Buchs, Switzerland) and 415 mg (3 mmol) of K_2CO_3 in 1.5 ml of DMSO are stirred 1.5 h at RT. After this time, the reaction mixture is treated with aqueous sat. $NaHCO_3$ and extracted with EtOAc. The organic layer is washed with aqueous sat. $NaHCO_3$ and with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica gel (hexane-EtOAc 4:1 to 0:1) to provide the title compound as a yellow solid. ES-MS: 322 $(M+H)^+$.

Example 51a

[1-(4-Amino-phenyl)-piperidin-4-ylmethyl]-carbamic acid tert-butyl ester

The title compound is obtained as described in Example **48a** starting with [1-(4-nitro-phenyl)-piperidin-4-ylmethyl]-carbamic acid tert-butyl ester (Example **51b**); ES-MS: 306 $(M+H)^+$; analytical HPLC: t_{ret}= 2.41 minutes (Grad 2).

Example 51b

[1-(4-Nitro-phenyl)-piperidin-4-ylmethyl]-carbamic acid tert-butyl ester

The title compound is obtained as described in Example **50b** starting with piperidin-4-ylmethyl-carbamic acid tert-butyl ester (Acros, Morris Plains, USA); ES-MS: 336 $(M+H)^+$.

The following compounds (see Table 11) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with the appropriate aniline as in Example **1e**.

Example 52 N-(4-amino-phenyl)-N-methyl-acetamide (Aldrich, Buchs, CH)

Example 53 (4-amino-phenyl)-methanesulfonamide (Lancaster, Newgate, UK)

Example 54 4-(2-azetidin-1-yl-ethyl)-phenylamine (Example **54a**)

Example 55 4-(2-pyrrolidin-1-yl-ethyl)-phenylamine (Example **55a**)

Example 56 (4-amino-3-chloro-phenyl)-acetonitrile (Example **56a**)

Example 57 (4-amino-2-chloro-phenyl)-acetonitrile (Example **57a**)

Example 58 (4-amino-3-methyl-phenyl)-acetonitrile (Example **58a**)

Example 59 (4-amino-2-methyl-phenyl)-acetonitrile (Example **59a**)

Example 60 (3-amino-phenyl)-acetonitrile (Example **60a**)

Table 11

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
52	2-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethylamine	418	2.45 Grad 2
53	N-Methyl-C-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-methanesulfonamide	454	2.42 Grad 2
54	1-[4-(2-Azetidin-1-yl-ethyl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	430	2.27 Grad 2
55	8-Pyridin-3-ylethynyl-1-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-1H-imidazo[4,5-c]quinoline	444	2.29 Grad 2

56	[3-Chloro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	420	2.71 Grad 2
57	[2-Chloro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	420	2.69 Grad 2
58	[3-Methyl-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	400	2.61 Grad 2
59	[2-Methyl-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	400	2.64 Grad 2
60	[3-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	386	5.63 Grad 3

Example 54a

4-(2-Azetidin-1-yl-ethyl)-phenylamine

The title compound is obtained as described in Example **48b** starting with 1-[2-(4-nitro-phenyl)-ethyl]-azetidine (Example **54b**); ES-MS: 177 $(M+H)^+$.

Example 54b

1-[2-(4-Nitro-phenyl)-ethyl]-azetidine

The title compound is obtained as described in Example **48c** starting with azetidine (Fluka, Buchs, CH); ES-MS: 207 $(M+H)^+$; analytical HPLC: t_{ret}= 2.28 minutes (Grad 2).

Example 55a

4-(2-Pyrrolidin-1-yl-ethyl)-phenylamine

The title compound is obtained as described in Example **48b** starting with 1-[2-(4-nitro-phenyl)-ethyl]-pyrrolidine (Example **55b**); ES-MS: 191 $(M+H)^+$.

Example 55b

1-[2-(4-Nitro-phenyl)-ethyl]-pyrrolidine

The title compound is obtained as described in Example **48c** starting with pyrrolidine (Fluka, Buchs, Switz.); ES-MS: 221 $(M+H)^+$; analytical HPLC: t_{ret}= 2.34 minutes (Grad 1).

Example 56a

(4-Amino-3-chloro-phenyl)-acetonitrile

2.86 g (21 mmol) of *N*-chlorosuccinimide are added to a stirred solution of 2.67 g (20 mmol) of (4-amino-phenyl)-acetonitrile (Aldrich, Buchs, CH) in 30 mL of isopropanol. The solution is refluxed for 1 h and then the solvent is removed *in vacuo*. The crude product is dissolved in EtOAc and water. The layers are separated and the organic layer is washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue is purified by chromatography on silica eluting with dichloromethane to afford the title compound; ES-MS: 167 $(M+H)^+$.

Example 57a

(4-Amino-2-chloro-phenyl)-acetonitrile

2.55 g (13 mmol) of (2-chloro-4-nitro-phenyl)-acetonitrile (Example **57b**) and 1 g of Raney-Ni are shacked in 75 mL of MeOH under 1.1 bar of H_2 for 7 h at RT. After completion of the reaction, the catalyst is filtered-off and the filtrate is evaporated to dryness. The residue is purified by flash chromatography on silica gel (hexane-EtOAc 10:1 to 2:1) to give the title compound as a yellowish solid: ES-MS: 167 $(M+H)^+$; analytical HPLC: t_{ret}= 2.11 minutes (Grad 1).

Example 57b

(2-Chloro-4-nitro-phenyl)-acetonitrile

2.94 g (26 mmol) of ethyl cyanoacetate (Fluka, Buchs, CH) and 1.66 g (26 mmol) of KOH in 8 ml of DMSO are stirred for 1 h, then 3.51 g (20 mmol) of 2-chloro-1-fluoro-4-nitro-benzene (Aldrich, Buchs, CH) are added and the reaction mixture is stirred for 7.5 h at RT. A solution of 37% aqueous HCl and 5.6 ml of acetic acid is added and the reaction mixture is heated for 3 h at reflux, then quenched with H_2O and extracted with diethylether (2×). The combined organic layers are washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica gel (hexane-EtOAc

10:1 to 6:1) to give the title compound as a gel solid: ES-MS: 195 $(M-H)^-$; analytical HPLC: t_{ret}= 4.01 minutes (Grad 1).

Example 58a

(4-Amino-3-methyl-phenyl)-acetonitrile

1.13 g (6.4 mmol) of (3-methyl-4-nitro-phenyl)-acetonitrile (Example **58b**) and 110 mg of Pd 5% on charcoal are shacked in 30 mL of MeOH under 1.1 bar of H_2 for 30 min. After completion of the reaction, the catalyst is filtered-off and the filtrate is evaporated *in vacuo* to dryness to provide the title compound as an orange solid. ES-MS: 147 $(M+H)^+$; analytical HPLC: t_R = 1.73 minutes (Grad 2).

Example 58b

(3-Methyl-4-nitro-phenyl)-acetonitrile

The title compound is obtained as described in Example **57b** starting with 4-fluoro-2-methyl-1-nitro-benzene (Aldrich, Buchs, Switzerland); ES-MS: 175 $(M-H)^-$; analytical HPLC: t_{ret}= 3.90 minutes (Grad 1).

Example 59a

(4-Amino-2-methyl-phenyl)-acetonitrile

The title compound is obtained as described in Example **58a** starting with (2-methyl-4-nitro-phenyl)-acetonitrile (Example 59b); ES-MS: 147 $(M+H)^+$; analytical HPLC: t_{ret}= 1.75 minutes (Grad 2).

Example 59b

(2-Methyl-4-nitro-phenyl)-acetonitrile

The title compound is obtained as described in Example **57b** starting with 4-fluoro-3-methyl-1-nitro-benzene (Aldrich, Buchs, Switzerland); ES-MS: 175 $(M-H)^-$; analytical HPLC: t_{ret}= 3.91 minutes (Grad 1).

Example 60a

(3-Amino-phenyl)-acetonitrile

The title compound is obtained by hydrogenation of 3-nitrophenylacetonitrile (Aldrich, Buchs, Switzerland) as described in Example **48a**; ES-MS: 133 $(M+H)^+$.

The following compounds (see Table 12) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 4-(2-dimethylamino-ethyl)-phenylamine (Example **61a**) as in Example **1e,** and using the following reagents as in Example **1g**.

Example 61 triethylorthoformate (Fluka, Buchs, Switzerland);

Example 62 triethylorthoacetate (Fluka, Buchs, Switzerland) as in Example **32**;

Example 63 tetramethylorthocarbonate (Aldrich, Buchs, Switzerland) as in Example **45a**; and

Example 64 dichloromethylene dimethylimmonium chloride (Fluka, Buchs, Switzerland) (Example **64a**).

Table 12

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
61	Dimethyl-{2-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-amine	418	2.22 Grad 2
62	Dimethyl-{2-[4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-amine	432	2.26 Grad 2
63	{2-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-dimethyl-amine	448	2.29 Grad 2
64	{1-[4-(2-Dimethylamino-ethyl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinolin-2-yl}-dimethyl-amine	461	5.22 Grad 3

Example 61a

4-(2-Dimethylamino-ethyl)-phenylamine

The title compound is obtained as described in Example **48b** starting with dimethyl-[2-(4-nitro-phenyl)-ethyl]-amine (Example **61b**); ES-MS: 179 $(M+H)^+$.

Example 61b

Dimethyl-[2-(4-nitro-phenyl)-ethyl]-amine

The title compound is obtained as described in Example **48c** starting with 5.6 M dimethylamine in EtOH (Fluka, Buchs, Switzerland); ES-MS: 165 $(M+H)^+$; analytical HPLC: t_{ret}= 1.86 minutes (Grad 1).

Example 64a

{8-Bromo-1-[4-(2-dimethylamino-ethyl)-phenyl]-1H-imidazo[4,5-c]quinolin-2-yl}-dimethyl-amine

193 mg (0.5 mmol) of 6-bromo-N-4-[4-(2-dimethylamino-ethyl)-phenyl]-quinoline-3,4-diamine, which was obtained as described in Example **1** reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 4-(2-dimethylamino-ethyl)-phenylamine (Example **61a**) as in Example **1e**, are dissolved in 5 ml of NMP and 251 mg (1.5 mmol) of dichloromethylene dimethylimmonium chloride (Fluka, Buchs, Switzerland) are added to the stirred solution. The mixture is stirred for 15 min at RT, and then 50 ml of EtOAc are added. The organic phase is washed with 0.1 N aqueous NaOH and water, dried over $MgSO_4$, filtered and evaportated to dryness. The residue is purified by medium-pressure liquid chromatography to provide the title compound. ES-MS: 437.5, 439.4 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 5.25 minutes (Grad 3).

The following compounds (see Table 46) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 4-(4-ethyl-piperazin-1-yl)-phenylamine (Acros, Morris Plains, USA) as in Example **1e**, and with a cyclisation reaction as in Example **1g** or Example **32**.

Table 13

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
65	1-[4-(4-Methyl-piperazin-1-yl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	445	2.25 Grad 2

66	2-Methyl-1-[4-(4-methyl-piperazin-1-yl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	459	2.28 Grad 2

Example 67

2-Methyl-1-[4-(4-methyl-piperazin-1-yl)-phenyl]-8-(1-oxy-pyridin-3-ylethynyl)-1H-imidazo[4,5-c]quinoline

The title compound is obtained as in Example **66** using 3-ethynyl-pyridine 1-oxide (Example **67a**) instead of 3-ethynyl-pyridine; ES-MS: 475 $(M+H)^+$; analytical HPLC: t_{ret}= 2.24 minutes (Grad 2).

Example 67a

3-Ethynyl-pyridine 1-oxide

To 400 mg (3.88 mmol) of 3-ethynyl-pyridine (Fluka, Buchs, Switzerland) in 40 ml of CH_2Cl_2 cooled with an ice-bath are added 1.41 g (4.65 mmol) of 57% *meta*-chloroperbenzoic acid. The reaction is then stirred 1 h at 0 °C and 3 h at RT. The reaction mixture is treated with aqueous sat. Na_2CO_3 and extracted with CH_2Cl_2. The organic layer is washed with aqueous sat. Na_2CO_3 and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica gel (CH_2Cl_2-MeOH 99:1 to 94:6) to provide the title compound as an off-white solid; analytical HPLC: t_{ret}= 1.67 minutes (Grad 2).

The following compounds (see Table 14) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 4-(4-methyl-piperazin-1-ylmethyl)-phenylamine (Example **68a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g** or Example **64**.

Table 14

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
68	1-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	459	4.97 Grad 3
69	Dimethyl-{1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinolin-2-yl}-amine	502	5.11 Grad 3

Example 68a

4-(4-Methyl-piperazin-1-ylmethyl)-phenylamine

The title compound is obtained by hydrogenation of 1-methyl-4-(4-nitro-benzyl)-piperazine (Example **68b**) as described in Example **67a**; ES-MS: 206 $(M+H)^+$.

Example 68b

1-Methyl-4-(4-nitro-benzyl)-piperazine

To a solution of 3 g (13.9 mmol) of 4-nitrobenzyl bromide (Flukla, Buchs, Switzerland) in 10 ml of DMF are added 3.08 ml (27.8 mmol) of N-methylpiperazine and 4.8 g (34.7 mmol) of K_2CO_3, and the mixture is stirred for 4.5 h at 80 °C. After this time, 150 ml of EtOAc are added and the solution is washed with water, dried over $MgSO_4$, filtered and evaporated to dryness to provide the title compound. ES-MS: 236 $(M+H)^+$.

The following compounds (see Table 15) are prepared as described in Example 1 by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 3-fluoro-4-(4-methyl-piperazin-1-yl)-phenylamine (Example **70a**) as in Example **1e** and with a cyclisation reaction as in Example **1g,** Example **32** or Example **45**.

Table 15

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
70	1-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	463	2.35 Grad 2
71	1-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-2-methyl-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	477	2.36 Grad 2
72	1-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-2-methoxy-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	493	2.40 Grad 2

Example 70a

3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenylamine

The title compound is obtained as described in Example **50a** starting with 1-(2-fluoro-4-nitro-phenyl)-4-methyl-piperazine (Example **70b**); ES-MS: 210 $(M+H)^+$.

Example 70b

1-(2-Fluoro-4-nitro-phenyl)-4-methyl-piperazine

The title compound is obtained as described in Example **50b** starting with 3,4-difluoro-nitrobenzene (Fluka, Buchs, Switzerland) and N-methylpiperazine (Fluka, Buchs, Switzerland); ES-MS: 240 $(M+H)^+$; analytical HPLC: t_{ret}= 2.47 minutes (Grad 2).

The following compounds (see Table 16) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with the required aniline.

Example 73 4-(4-amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **73a**); and

Example 74 4-(4-amino-2-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **74a**).

Table 16

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
73	2-Methyl-1-(4-piperazin-1-yl-phenyl)-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	445	2.30 Grad 2
74	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-methyl-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline	463	2.34 Grad 2

Example 73a

4-(4-Amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

The title compound is obtained as described in Example **50a** starting with 4-(4-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **73b**); ES-MS: 278 $(M+H)^+$; analytical HPLC: t_{ret}= 2.71 minutes (Grad 2).

Example 73b

4-(4-Nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

The title compound is obtained as described in Example **50b** starting with piperazine-1-carboxylic acid tert-butyl ester (Fluka, Buchs, CH); ES-MS: 308 $(M+H)^+$.

Example 74a

4-(4-Amino-2-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

The title compound is obtained as described in Example **50a** starting with 4-(2-fluoro-4-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **74b**); ES-MS: 296 $(M+H)^+$; analytical HPLC: t_{ret}= 2.87 minutes (Grad 2).

Example 74b

4-(2-Fluoro-4-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

The title compound is obtained as described in Example **50b** starting with 3,4-difluoro-nitrobenzene (Fluka, Buchs, Switzerland); ES-MS: 326 $(M+H)^+$.

Example 75

1-[4-(4-Ethyl-piperazin-1-yl)-3-fluoro-phenyl]-2-methyl-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline

80 mg (0.173 mmol) of 1-(3-fluoro-4-piperazin-1-yl-phenyl)-2-methyl-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline (Example 74), 27 mg (0.173 mmol) of iodoethane and 34 mg (0.259 mmol) of ethyl-diisopropyl-amine in 2 ml CH_2Cl_2-MeOH (5:1) are stirred 5 days at RT and then 8 mg (0.052 mmol) of iodoethane are added and the reaction mixture stirred for 2 days at RT. The reaction mixture is quenched with aqueous sat. $NaHCO_3$ and extracted with EtOAc. The organic layer is washed with aqueous sat. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by prep. HPLC. The pure fractions are concentrated, basified with $NaHCO_3$ and extracted with EtOAc (3×). The organic layers are dried over $MgSO_4$, filtered and evaporated to dryness to give the title compound. ES-MS: 491 $(M+H)^+$; analytical HPLC: t_{ret}= 2.42 minutes (Grad 2).

The following compounds (see Table 50) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 5-amino-2-(4-methyl-piperazin-1-yl)-benzonitrile (Example **76a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 17

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
76	2-(4-Methyl-piperazin-1-yl)-5-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	470	2.33 Grad 2
77	2-(4-Methyl-piperazin-1-yl)-5-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	484	2.32 Grad 2
78	5-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(4-methyl-piperazin-1-yl)-benzonitrile	500	2.35 Grad 2
79	5-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(4-methyl-piperazin-1-yl)-benzonitrile	513	2.39 Grad 2

Example 76a

5-Amino-2-(4-methyl-piperazin-1-yl)-benzonitrile

The title compound is obtained as described in Example **50a** starting with 2-(4-methyl-piperazin-1-yl)-5-nitro-benzonitrile (Example **76b**); ES-MS: 217 $(M+H)^+$.

Example 76b

2-(4-Methyl-piperazin-1-yl)-5-nitro-benzonitrile

1 g (6.02 mmol) of 2-fluoro-5-nitro-benzonitrile (Aldrich, Buchs, Switzerland), 663 mg (6.62 mmol) of N-methylpyperazine (Fluka, Buchs, CH) and 2.5 g (18.1 mmol) of K_2CO_3 in 12 ml DMF are stirred for 30 min at rt, then the reaction mixture is evaporated to dryness. The residue is treated with water and extracted with EtOAc (2×). The combined organic layers are washed with aqueous sat. $NaHCO_3$ (3×), dried over $MgSO_4$, filtered and evaporated to dryness. The residue is purified by flash chromatography on silica gel (CH_2Cl_2-MeOH-NEt_3 196:4:1 to 193:7:1) to provide the title compound as a yellow solid: ES-MS: 247 $(M+H)^+$; analytical HPLC: t_{ret}= 2.38 minutes (Grad 2).

The following compounds (see Table 18) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 4-(4-amino-2-cyano-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **80a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 18

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
80	2-Piperazin-1-yl-5-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	456	2.30 Grad 2
81	5-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-piperazin-1-yl-benzonitrile	470	2.29 Grad 2
82	5-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-piperazin-1-yl-benzonitrile	486	2.32 Grad 2
83	5-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-piperazin-1-yl-benzonitrile	499	2.36 Grad 2

Example 80a

4-(4-Amino-2-cyano-phenyl)-piperazine-1-carboxylic acid tert-butyl ester

The title compound is obtained as described in Example **50a** starting with 4-(2-cyano-4-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **80b**); ES-MS: 303 $(M+H)^+$; analytical HPLC: t_{ret}= 2.99 minutes (Grad 2).

Example 80b

4-(2-Cyano-4-nitro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester SH-242

1 g (6.02 mmol) of 2-fluoro-5-nitro-benzonitrile (Aldrich, Buchs, Switzerland), 1.23 g (6.62 mmol) of piperazine-1-carboxylic acid tert-butyl este (Fluka, Buchs, Switzerland) and 1.17 g (9.3 mmol) of ethyldiisopropylamine in 5 ml DMSO are stirred for 30 min at RT, then the reaction mixture is treated with water and extracted with EtOAc (2×). The combined organic layers are washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness to give the title compound as a yellow solid: analytical HPLC: t_{ret}= 4.06 minutes (Grad 2).

The following compounds (see Table 19) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 3-amino-benzonitrile (Fluka, Buchs, Switzerland) s in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 19

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
84	3-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	372	5.68 Grad 3
85	3-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	386	5.68 Grad 3
86	3-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	402	5.76 Grad 3
87	3-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	415	5.78 Grad 3

Example 88

3-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzylamine

The title compound is obtained as described in Example **52** starting with 3-(8-bromo-imidazo[4,5-c]quinolin-1-yl)-benzylamine (Example **88a**); ES-MS: 376 $(M+H)^+$; analytical HPLC: t_{ret}= 2.17 minutes (Grad 2).

Example 88a

3-(8-Bromo-imidazo[4,5-c]quinolin-1-yl)-benzylamine

240 mg (0.687 mmol) of 3-(8-bromo-imidazo[4,5-c]quinolin-1-yl)-benzonitrile (intermediate in Example **88**; ES-MS: 350 $(M+H)^+$) and 0.1 g of Raney-Ni are shacked in 6 mL of THF-[MeOH/NH_3 (5%)] (1:1) under 1.1 bar of H_2 for 10 h at 42°C. After completion of the reaction, the catalyst is filtered-off and the filtrate is evaporated *in vacuo* to give the title compound as an off-white solid: ES-MS: 353, 355 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 2.19 minutes (Grad 2).

The following compounds (see Table 20) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 4-amino-benzonitrile (Fluka, Buchs, Switzerland) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 20

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
89	4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	372	5.72 Grad 3
90	4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	386	5.71 Grad 3
91	4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	402	5.83 Grad 3
92	4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	415	5.83 Grad 3

The following compounds (see Table X14) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with (4-amino-phenyl)-acetonitrile (Aldrich, Buchs, Switzerland) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **36**, Example **45**, Example **64** or Example **98a**.

Table 21

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
93	[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	386	2.52 Grad 2
94	[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	400	2.54 Grad 2
95	[4-(2-Ethyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	414	2.71 Grad 2
96	[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	416	2.63 Grad 2
97	[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	429	5.78 Grad 3
98	{4-[2-(3-Dimethylamino-propyl)-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile	471	5.28 Grad 3

Example 98a

{4-[8-Bromo-2-(3-dimethylamino-propyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile

33 mg (0.078 mmol) of {4-[8-bromo-2-(3-hydroxy-propyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile (Example **98b**) are dissolved in 3 ml of anydrous pyridine and the solution is cooled to -18 °C. To this solution, 69 mg (0.35 mmol) of p-toluenesulfonyl chloride are added and the mixture is stirred for 3 days at -18 °C. After this time, 50 ml of EtOAc are added and the solution is extracted with water. The organic phase is evaporated to dryness and the residue is dissolved in 2 ml of ethanol. To this solution, 0.28 ml (0.16 mmol) of dimethylamine are added and the mixture is refluxed for 1 h. After this time, the mixture is evaporated to dryness and the residue is purified by medium-pressure liquid chromatography to provide the title compound; ES-MS: 448, 450 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 5.62 minutes (Grad 3).

Example 98b

{4-[8-Bromo-2-(3-hydroxy-propyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile

0.23 ml (0.23 mmol) of borane tetrahydrofuran complex solution are added to a solution of 90 mg (0.21 mmol) of 3-[8-bromo-1-(4-cyanomethyl-phenyl)-1H-imidazo[4,5-c]quinolin-2-yl]-propionic acid (Example **98c**) in 5 ml of THF. The mixture is stirred for 4 h at room temperature. After this time, the reaction is quenched with 95 % TFA and the pH is then adjusted to 9-10 by addition of 2 N NaOH. The mixture is extracted with EtOAc and the organic phase is washed with water, dried over $MgSO_4$, filtered and evaporated to dryness to provide the title compound. ES-MS: 421, 423 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 5.95 minutes (Grad 3).

Example 98c

3-[8-Bromo-1-(4-cyanomethyl-phenyl)-1H-imidazo[4,5-c]quinolin-2-yl]-propionic acid

The title compound is obtained as described in Example **46a** using [4-(3-amino-6-bromo-quinolin-4-ylamino)-phenyl]-acetonitrile (intermediate in Example **93**; ES-MS: 353, 355 $(M+H)^+$, Br pattern) and succinaldehydic acid (Fluka, Buchs, Switzerland); ES-MS: 436.8 $(M+H)^+$; analytical HPLC: t_{ret}= 5.98 minutes (Grad 3).

The following compounds (see Table 22) are prepared as described in Example **92** by using the required alkyne as in Example **42** or Example **67**.

Table 22

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
99	{4-[8-(6-Morpholin-4-yl-pyridin-3-ylethynyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile	471	2.64 Grad 2
100	{4-[8-(1-Oxy-pyridin-3-ylethynyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile	402	2.49 Grad 2

The following compounds (see Table X16) are prepared as in Example **93** using [4-(4-amino-8-bromo-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile (Example **101a**) or [4-(8-bromo-4-methylamino-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile (Example **102a**).

Table 23

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
101	[4-(4-Amino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	401	2.60 Grad 2
102	[4-(4-Methylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	415	2.66 Grad 2

Example 101a

[4-(4-Amino-8-bromo-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile

172 mg (0.433 mmol) of [4-(8-bromo-4-chloro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile (Example **101b**) and 3 ml (6 mmol) of 2 M NH_3 in MeOH are heated in a microwave oven for 10 h at 130°C, then the rection mixture is evaporated to dryness. The residue is purified by flash chromatography on silica gel (CH_2Cl_2-MeOH 1:0 to 96:4) to provide the title compound as a brownish solid: ES-MS: 378, 380 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 2.96 minutes (Grad 2).

Example 101b

[4-(8-Bromo-4-chloro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile

300 mg (0.791 mmol) of [4-(8-bromo-5-oxy-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile (Example **101c**) and 364 mg (2.37 mmol) of $POCl_3$ in 8 ml toluene-DMF (39:1) are heated for 4 h at 70°C. The rection mixture is quenched with aqueous sat. $NaHCO_3$ and extracted with EtOAc (2×). The organic layers are washed wiht aqueous sat. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to provide the title compound as a brownish solid: ES-MS: 397, 399 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.81 minutes (Grad 2).

Example 101c

[4-(8-Bromo-5-oxy-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile

340 mg (0.936 mmol) of [4-(8-bromo-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile (intermediate in Example **93**; ES-MS: 363, 365 $M(+H)^+$), 119 mg (1.12 mmol) of Na_2CO3 and 312 mg (1.03 mmol) of 57% *meta*-chloroperbenzoic acid in 10 ml of chloroform are stirred for 20 h at RT. The rection mixture is quenched with aqueous sat. Na_2CO_3 and extracted with CH_2Cl_2 (2×). The organic layers are washed wiht brine, dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the title compound as an orange solid: ES-MS: 379, 381 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.06 minutes (Grad 2).

Example 102a

[4-(8-Bromo-4-methylamino-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile

The title compound is obtained as described in Example **101a** using 8 M methylamine in EtOH for 2 h at 120°C; ES-MS: 392, 394 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.00 minutes (Grad 2).

The following compounds (see Table 24) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with (4-amino-2-fluoro-phenyl)-acetonitrile (Example **103a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 24

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
103	[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	404	2.61 Grad 2
104	[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	418	2.61 Grad 2
105	[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile	434	2.69 Grad 2
106	[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-acetonitrile	447	2.69 Grad 2

Example 103a

(4-Amino-2-fluoro-phenyl)-acetonitrile

1.55 g (8.6 mmol) of (2-fluoro-4-nitro-phenyl)-acetonitrile (Example **103b**) and 160 mg of Pd 5% on charcoal are shacked in 45 mL of MeOH under 1.1 bar of H_2 for 4 h. After completion of the reaction, the catalyst is filtered-off and the filtrate is evaporated *in vacuo* to dryness to provide the title compound as a brown solid: analytical HPLC: t_R = 1.76 minutes (Grad 2).

Example 103b

(2-Fluoro-4-nitro-phenyl)-acetonitrile

1.59 g (10 mmol) of 3,4-difluoro-1-nitrobenzene, 1.9 g (13.8 mmol) of finely-powdered K_2CO_3, 16.6 mg (0.1 mmol) of KI and 1.24 g (11 mmol) of ethyl cyanoacetate in 10 mL DMF are stirred for 4 h at RT, and then 1 h at 50°C and 1 h at 100°C. The reaction mixture is quenched with aqueous 1 M citric acid and extracted with EtOAc. The combined organic layers are washed with brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue is treated with 1 mL of HCl (37%) in 10 mL of H_2O-acetic acid (3:1) for 8 h at 100°C. After this time, the reaction mixture is quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The combined organic layers are washed with aqueous $NaHCO_3$, brine and dried over $MgSO_4$. The organic phase is evaporated *in vacuo* to dryness to give the title compound as a pale yellow solid: ES-MS: 179 $(M-H)^-$,analytical HPLC: t_R = 3.69 minutes (Grad 2);

The following compounds (see Table 25) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 2-(4-amino-phenyl)-2-methyl-propionitrile (Example **107a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32** or Example **45**.

Table 25

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
107	2-Methyl-2-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile	414	2.86 Grad 2
108	2-Methyl-2-[4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile	428	2.85 Grad 2
109	2-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-2-methyl-propionitrile	444	2.92 Grad 2

Example 107a

(2-(4-Amino-phenyl)-2-methyl-propionitrile

3.8 g (20 mmol) of 2-methyl-2-(4-nitro-phenyl)-propionitrile (Example **10b**) and 1 g of Raney-Ni are shacked in 50 mL of THF-MeOH (1:1) under 1.1 bar of H_2 for 4 h at RT. After completion of the reaction, the catalyst is filtered-off and the filtrate is evaporated to dryness. The residue is purified by flash chromatography on silica gel (hexane-EtOAc 3:1 to 1:2) to give the title compound as an oil: ES-MS: 161 $(M+H)^+$; analytical HPLC: t_{ret}= 2.13 minutes (Grad 2).

Example 107b

2-Methyl-2-(4-nitro-phenyl)-propionitrile

To 4.5 g (27.8 mmol) of (4-nitro-phenyl)-acetonitrile (Fluka, Buchs, Switzerland), 500 mg (1.55 mmol) of tetrabutylammonium bromide (Fluka, Buchs, Switzerland) and 13 g (91.6 mmol) of iodomethane in 37.5 mL of CH_2Cl_2 are added 3 g (75 mmol) of NaOH in 37.5 ml of water. The reaction mixture is stirred for 12 h at RT, then the organic layer is separated and dried over $MgSO_4$, and evaporated to dryness. The residue is dissolved in diethylether and treated with black charcoal for 30 min, filtered over Celite and evaporated *in vacuo* to give the title compound as a pale yellow solid: analytical HPLC: t_{ret}= 3.60 minutes (Grad 2).

The following compounds (see Table 26) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 2-(4-amino-2-fluoro-phenyl)-2-methyl-propionitrile (Example **109a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32** or Example **64**.

Table 26

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
110	2-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-2-methyl-propionitrile	432	2.86 Grad 2
111	2-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-2-methyl-propionitrile	446	2.88 Grad 2
112	2-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-2-methyl-propionitrile	475	2.95 Grad 2

Example 110a

2-(4-Amino-2-fluoro-phenyl)-2-methyl-propionitrile

The title compound is obtained as described in Example **48a** starting with 2-(2-fluoro-4-nitro-phenyl)-2-methyl-propionitrile (Example **110b**); ES-MS: 251 $(M+H)^+$; analytical HPLC: t_{ret}= 2.87 minutes (Grad 2).

Example 110b

2-(2-Fluoro-4-nitro-phenyl)-2-methyl-propionitrile

The title compound is obtained as described in Example **107b** starting with (2-fluoro-4-nitro-phenyl)-acetonitrile (Example **103a**); analytical HPLC: t_{ret}= 3.64 minutes (Grad 2).

The following compounds (see Table 27) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 3-(4-amino-phenyl)-propionitrile (Example **113a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 27

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
113	3-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile	400	2.57 Grad 2
114	3-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrileBAE852/SH-137	414	2.63 Grad 2
115	3-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile	430	2.71 Grad 2
116	3-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile	443	5.88 Grad 3

Example 113a

3-(4-Amino-phenyl)-propionitrile

0.78 g (4.4 mmol) of 3-(4-nitro-phenyl)-propionitrile (Example **113b**) are dissolved in 40 mL of MeOH:THF (1:1) and hydrogenated at RT in the presence of 50 mg of Pd-C 10%. After completion of the reaction, the catalyst is filtered-off and washed with methanol. The organic solvent is evaporated to dryness to provide the title compound; ES-MS: 147.3 $(M+H)^+$.

Example 113b

3-(4-Nitro-phenyl)-propionitrile

3.45 of (15 mmol) of 4-nitrophenethyl bromide are dissolved in 50 mL of ethanol and 0.81 g (16.5 mmol) of sodium cyanide are added. The solution is stirred for 4 h at RT and then evaporated to dryness. The crude compound is dissolved in 100 mL of EtOAc, and the organic solution is extracted with water, brine, dried over $MgSO_4$ and evaporated to dryness. The crude compound is purified by medium-pressure liquid chromatography to provide the title compound; ES-MS: 175.3 ($M-H)^-$.

The following compounds (see Table 28) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 1-(4-amino-2-fluoro-phenyl)-pyrrolidin-2-one (Example **117a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g,** Example **32**, Example **45** or Example **64.**

Table 28

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
117	1-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one	448	2.56 Grad 2
118	1-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one	462	2.58 Grad 2
119	1-[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one	478	2.66 Grad 2
120	1-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-pyrrolidin-2-one	491	2.67 Grad 2

Example 117a

1-(4-Amino-2-fluoro-phenyl)-pyrrolidin-2-one

The title compound is obtained as described in Example **48a** starting with 1-(2-fluoro-4-nitro-phenyl)-pyrrolidin-2-one (Example **177b**); ES-MS: 195 $(M+H)^+$; analytical HPLC: t_{ret}= 1.91 minutes (Grad 2).

Example 177b

1-(2-Fluoro-4-nitro-phenyl)-pyrrolidin-2-one

To 468 mg (5.5 mmol) of 2-pyrrolidone (Fluka, Buchs, Switzerland) in 10 ml of DMF cooled with an ice-bath are added 240 mg (5.5 mmol) of 55% NaH in oil. The reaction mixture is stirred for 30 min at 0 °C and for 30 min at RT, then are added 795 mg (5 mmol) of 3,4-difluoronitrobenzene (Aldrich, Buchs, Switzerland) and the reaction mixture is stirred for 1 h at RT. The rection mixture is quenched with 1 M aqueous HCl and extracted with EtOAc (2×). The organic layers are washed wiht aqueous sat. $NaHCO_3$ and with brine (3×), dried over $MgSO_4$, filtered and evaporated. The residue is purified by flash chromatography on silica gel (hexane-EtOAc 5:1 to 1:3) to give the title compound; ES-MS: 225 $(M+H)^+$; analytical HPLC: t_{ret}= 2.99 minutes (Grad 2).

The following compounds (see Table 29) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 1-(4-amino-

phenyl)-pyrrolidin-2-one (Example **121a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 29

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
121	1-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one	430	2.56 Grad 2
122	1-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one	444	2.60 Grad 2
123	1-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one	460	2.66 Grad 2
124	1-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one	473	2.70 Grad 2

Example 121a

1-(4-Amino-phenyl)-pyrrolidin-2-one

The title compound is obtained as described in Example **48a** starting with 1-(4-nitro-phenyl)-pyrrolidin-2-one (Acros, Basel, CH); ES-MS: 177 $(M+H)^+$; analytical HPLC: t_{ret}= 2.71 minutes (Grad 2).

The following compounds (see Table 30) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 5-amino-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile (Example **125a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 30

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
125	2-(2-Oxo-pyrrolidin-1-yl)-5-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	455	2.47 Grad 2
126	5-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile	469	2.48 Grad 2
127	5-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile	485	2.55 Grad 2
128	5-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile	498	2.56 Grad 2

Example 125a

5-Amino-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile

The title compound is obtained as described in Example **48a** starting with 5-nitro-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile (Example **125b**); ES-MS: 202 $(M+H)^+$; analytical HPLC: t_{ret}= 2.09 minutes (Grad 2).

Example 125b

5-Nitro-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile

The title compound is obtained as described in Example **117b** starting with 2-fluoro-5-nitro-benzonitrile (Aldrich, Buchs, Switzerland) ; ES-MS: 232 $(M+H)^+$; analytical HPLC: t_{ret}= 2.80 minutes (Grad 2).

The following compounds (see Table 31) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 3-(4-amino-2-fluoro-phenyl)-oxazolidin-2-one (Example **129a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 31

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
129	3-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one	450	2.51 Grad 2
130	3-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one	464	2.52 Grad 2
131	3-[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one	480	2.60 Grad 2
132	3-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-oxazolidin-2-one	493	2.62 Grad 2

Example 129a

3-(4-Amino-2-fluoro-phenyl)-oxazolidin-2-one

The title compound is obtained as described in Example **48a** starting with 3-(2-fluoro-4-nitro-phenyl)-oxazolidin-2-one (Example **129b**); ES-MS: 197 $(M+H)^+$; analytical HPLC: t_{ret}= 1.66 minutes (Grad 2).

Example 129b

3-(2-Fluoro-4-nitro-phenyl)-oxazolidin-2-one

The title compound is obtained as described in Example **117b** starting with 2-oxazolidinone (Fluka, Buchs, Switzerland); ES-MS: 225 $(M-H)^-$; analytical HPLC: t_{ret}= 2.90 minutes (Grad 2).

The following compounds (see Table 32) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 3-(4-amino-phenyl)-oxazolidin-2-one (Example **132a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32** or Example **45**.

Table 32

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
133	3-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one	432	2.50 Grad 2
134	3-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one	446	2.52 Grad 2
135	3-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one	462	2.60 Grad 2

Example 133a

3-(4-Amino-phenyl)-oxazolidin-2-one

The title compound is obtained as described in Example **48a** starting with 3-(4-nitro-phenyl)-oxazolidin-2-one (Example **133b**); ES-MS: 179 $(M+H)^+$; analytical HPLC: t_{ret}= 1.46 minutes (Grad 2).

Example 133b

3-(4-Nitro-phenyl)-oxazolidin-2-one

The title compound is obtained as described in Example **117b** starting with 2-oxazolidinone (Fluka, Buchs, Switzerland) and 4-fluoro-nitrobenzene (Aldrich, Buchs, Switzerland); analytical HPLC: t_{ret}= 2.98 minutes (Grad 2).

The following compounds (see Table 33) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 1-(4-amino-2-fluoro-phenyl)-pyrrolidine-2,5-dione (Example **136a**) as in Example **1e**, and with a cyclisation reaction as in Example **1g**, Example **32**, Example **45** or Example **64**.

Table 33

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
136	1-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione	462	5.65 Grad 3
137	1-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione	476	5.71 Grad 3
138	1-[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione	492	5.50 Grad 3
139	1-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-pyrrolidine-2,5-dione	505	5.57 Grad 3

Example 136a

1-(4-Amino-2-fluoro-phenyl)-pyrrolidine-2,5-dione

The title compound is obtained by reduction of 1-(2-fluoro-4-nitro-phenyl)-pyrrolidine-2,5-dione (Example 136b) as described in Example 58a. ES-MS: 209.2 $(M+H)^+$; analytical HPLC: t_{ret}= 4.69 minutes (Grad 3).

Example 136b

1-(2-fluoro-4-nitro-phenyl)-pyrrolidine-2,5-dione

The title compound is obtained as described in Example 50b using 1,2-difluoro-4-nitro-benzene (Aldrich, Buchs, Switzerland) and pyrrolidine-2,5-dione(Aldrich, Buchs, Switzerland) in DMSO at 100 °C. ES-MS: 238.1 $(M-H)^-$; analytical HPLC: t_{ret}= 6.52 minutes (Grad 3).

The following compounds (see Table 34) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 4-(4-amino-2-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **74a**), and with a cyclisation reaction as in Example **1g**, Example **45** or Example **64**.

Table 34

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
140	1-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione	449	2.34 Grad 2
141	1-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione	479	2.38 Grad 2
142	1-[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione	492	2.43 Grad 2

The following compounds (see Table 35) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 4-(4-amino-2-fluoro-phenyl)-piperazin-2-one (Example **143a**) as in Example **1e**, with cyclisation reaction as in Example **1g** or Example **32**, and with or without a subsequent introduction of an ethyl (Example **145a**) or a methyl group (Example **147a**).

Table 35

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
143	4-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperazin-2-one	463	2.48 Grad 2
144	1-Ethyl-4-[2-fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperazin-2-one	477	2.50 Grad 2
145	1-Ethyl-4-[2-fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperazin-2-one	491	2.71 Grad 2
146	1-Ethyl-4-[2-fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperazin-2-one	505	2.73 Grad 2
147	4-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-1-methyl-piperazin-2-one	477	2.60 Grad 2
148	4-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-1-methyl-piperazin-2-one	491	2.62 Grad 2

Example 143a

4-(4-Amino-2-fluoro-phenyl)-piperazin-2-one

The title compound is obtained as described in Example **48a** starting with 4-(2-fluoro-4-nitro-phenyl)-piperazin-2-one (Example **143b**); ES-MS: 210 $(M+H)^+$; analytical HPLC: t_{ret}= 1.41 minutes (Grad 2).

Example 143b

4-(2-Fluoro-4-nitro-phenyl)-piperazin-2-one

The title compound is obtained as described in Example **50b** starting with 3,4-difluoro-nitrobenzene (Fluka, Buchs, Switzerland) and piperazin-2-one (Avocado, Heysham, UK); ES-MS: 238 $(M-H)^-$.

Example 145a

4-[4-(8-Bromo-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-1-ethyl-piperazin-2-one

200 mg (0.454 mmol) 4-[4-(8-bromo-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-piperazin-2-one (intermediate in Example **143**; ES-MS: 440, 442 $(M+H)^+$, Br pattern) and 2 ml DMF are treated under Ar with 22 mg (0.5 mmol) of 55% NaH in oil. The reaction mixture is stirred for 2 h at RT, then 85 mg (0.545 mmol) iodoethane (Fluka, Buchs, CH) are added. The reaction mixture is stirred 12 h at RT. After this time, the reation mixture is quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer is washed with brine (3×) and dried over $MgSO_4$, filtered and evaporated to dryness. The residue is preabsorbed on silica gel and purified by flash crhomatography on silica gel (CH_2Cl_2-MeOH 1:0 to 92:8) to provide the title compound: ES-MS: 468, 470 $(M+H)^+$; analytical HPLC: t_{ret}= 2.92 minutes (Grad 2).

Example 147a

4-[4-(8-Bromo-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-1-methyl-piperazin-2-one

The title compound is obtained as described in Example **145a** using iodomethane (Fluka, Buchs, CH); ES-MS: 454, 456 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 2.76 minutes (Grad 2).

The following compounds (see Table **69**) are prepared as described in Example **1** by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with 5-amino-2-cyanomethyl-benzonitrile (Example **149a**) as in Example **1e**, and with or without a subsequent introduction of two methyl groups (Example **150a**).

Table 36

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
149	2-Cyanomethyl-5-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	425	2.52 Grad 2
150	2-(Cyano-dimethyl-methyl)-5-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile	453	2.75 Grad 2

Example 149a

5-Amino-2-cyanomethyl-benzonitrile

The title compound is obtained as described in Example **48a** starting with cyano-(2-cyano-4-nitro-phenyl)-acetic acid benzyl este (Example **149b**); ES-MS: 157 $(M-H)^-$, Br pattern; analytical HPLC: t_{ret}= 2.10 minutes (Grad 2).

Example 149b

Cyano-(2-cyano-4-nitro-phenyl)-acetic acid benzyl ester

1.0 g (6.02 mmol) of 2-fluoro-5-nitro-benzonitrile (Aldrich, Buchs, CH), 1.15 g (8.31 mmol) of finely-powdered K_2CO_3, 10 mg (0.06 mmol) of KI and 1.16 g (6.62 mmol) of benzyll cyanoacetate in 6 mL DMF are stirred under Ar for 5 h at 50°C and 1 h at 100°C. The reaction mixture is quenched with H_2O and extracted with EtOAc (2×). The combined organic layers are washed with brine (3×), dried over $MgSO_4$, filtered and evaporated to dryness to provide the title compound: ES-MS: 320 $(M-H)^-$; analytical HPLC: t_{ret}= 3.92 minutes (Grad 2).

Example 150a

5-(8-Bromo-2-methyl-imidazo[4,5-c]quinolin-1-yl)-2-(cyano-dimethyl-methyl)-benzonitrile

830 mg (2.06 mmol) of 5-(8-bromo-2-methyl-imidazo[4,5-c]quinolin-1-yl)-2-cyanomethyl-benzonitrile (intermediate in Example **149**; ES-MS: 402, 404 $(M+H)^+$, Br pattern) in 20 ml of DMF are treated under Ar with 198 mg (2.27 mmol) of 55% NaH in oil. The reaction mixture is stirred for 1 h at RT and then is cooled with an ice-bath and 142 ul (2.27 mmol) iodomethane (Fluka, Buchs, CH) are added. The reaction mixture is stirred for 1 h at RT, then are added 198 mg (2.27 mmol) 55% NaH in oil. The reaction mixtures is stirred for 1 h at RT, then is cooled with an ice-bath and 142 ul (2.27 mmol) iodomethane are added and the reaction mixture is stirred for 1 h at RT. After this time, the reaction mixture is quenched with brine and is extracted with EtOAc. The organic layer is washed with brine, dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by medium-pressure liquid chromatography to provide the title compound: ES-MS: 430, 432 $(M+H)^+$; analytical HPLC: t_{ret}= 3.09 minutes (Grad 2).

The following compounds (see Table 37) are prepared as described in Example 1 by reacting 6-bromo-4-chloro-3-nitro-quinoline (Example **1c**) with the appropriate aniline as in Example **1e**, and with cyclisation as described in Example **151a** and subsequent methylation as described in Example **151b**.

Example 151 4-fluoro-aniline (Fluka, Buchs, CH);

Example 152 4-ethyl-aniline (Fluka, Buchs, CH);

Example 153 3-methoxy-aniline (Fluka, Buchs, CH);

Example 154 4-methoxy-aniline (Fluka, Buchs, CH);

Example 155 3,4,5-trimethoxy-aniline (Fluka, Buchs, CH);

Example 156 (2-(4-amino-phenyl)-2-methyl-propionitrile (Example **107b**);

Example 157 3-(4-amino-phenyl)-oxazolidin-2-one (Example **133a**);

Example 158 3-(4-amino-2-fluoro-phenyl)-oxazolidin-2-one (Example **129a**);

Example 159 4-(4-amino-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **73a**);

Example 160 4-(4-amino-2-fluoro-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (Example **74a**); and

Example 161 (4-amino-phenyl)-carbamic acid tert-butyl ester (Fluka, Buchs, CH).

Table 37

Example	Compound name	ES-MS $(M+H)^+$	t_{ret} [min]
151	1-(4-Fluoro-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	395	2.62 Grad 2
152	1-(4-Ethyl-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	405	2.95 Grad 2
153	1-(3-Methoxy-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	407	2.65 Grad 2
154	1-(4-Methoxy-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	407	2.64 Grad 2
155	3-Methyl-8-pyridin-3-ylethynyl-1-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	467	2.59 Grad 2
156	2-Methyl-2-[4-(3-methyl-2-oxo-8-pyridin-3-ylethynyl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile	444	2.83 Grad 2
157	3-Methyl-1-[4-(2-oxo-oxazolidin-3-yl)-phenyl]-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	462	2.48 Grad 2
158	1-[3-Fluoro-4-(2-oxo-oxazolidin-3-yl)-phenyl]-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	480	2.53 Grad 2
159	3-Methyl-1-(4-piperazin-1-yl-phenyl)-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	461	2.29 Grad 2
160	1-(3-Fluoro-4-piperazin-1-yl-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	479	2.34 Grad 2
161	3-Methyl-1-(4-methylamino-phenyl)-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one	406	2.52 Grad 2

Example 151a

8-Bromo-1-(4-fluoro-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one

To a solution of 1.63 g (4.19 mmol) of 6-bromo-N*4*-(4-fluoro-phenyl)-quinoline-3,4-diamine (ES-MS: 332, 334 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.10 minutes (Grad 2)) and 596 mg (5.89 mmol) of triehtylamine in 50 ml of CH_2Cl_2 cooled with an ice-bath are added, under argon and over 10 min, 1.07 g (5.4 mmol) of trichloromethyl chloroformate (Fluka, Buchs, CH) in 50 ml CH_2Cl_2. The reaction mixture is stirred for 30 min at 0°C. After this time, the reaction mixture is quenched with brine and extracted with CH_2Cl_2 (3×). The combined organic layers are washed with brine (3×), dried over Na_2SO_4, filtered and evaporated to dryness to provide the title compound: ES-MS: 358, 360 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 2.92 minutes (Grad 2).

Example 151b

8-Bromo-1-(4-fluoro-phenyl)-3-methyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one

1.51 g (4.22 mmol) of 8-bromo-1-(4-fluoro-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one (Example **151a**), 136 mg (0.422 mmol) of tetrabutylammonium bromide, 898 mg (6.32 mmol) of iodomethane (Fluka, Buchs, CH) in 100 ml of CH_2Cl_2 are treated with a solution of 253 mg (6.32 mmol) of NaOH in 50 ml H_2O. The reaction mixture is stirred 13 h at RT. After this time, the reaction mixture is extracted with CH_2Cl_2(2×). The combine organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue is preabsrobed on silica gel and is purified by flash chromatography (CH_2Cl_2-MeOH 1:0 to 93:7) to provide the title compound: ES-MS: 372, 374 $(M+H)^+$, Br pattern; analytical HPLC: t_{ret}= 3.01 minutes (Grad 2).

Example 162

N-Methyl-N-[4-(3-methyl-2-oxo-8-pyridin-3-ylethynyl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetamide

110 mg (0.214 mmol) of 3-methyl-1-(4-methylamino-phenyl)-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one·3 HCl (Example **161** HCl salt) and 108 mg (1.07 mmol) of triethylamine in 2 ml of CH_2Cl_2 are stirred 15 min. The reaction mixture is treated with 25.4

mg (0.324 mmol) of acetyl chloride (Fluka, Buchs, CH). The reaction mixture is stirred 3 h at RT. After this time, 16.6 mg (0.211 mmol) of acetyl chloride are added and the reaction mixture is stirred for 2 at RT, then the reaction mixture is quenched with brine and is extracted with CH_2Cl_2. The combine organic layers are washed with sat. aqueous $NaHCO_3$, with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue is pre-absorbed on silica gel and is purified by flash chromatography (CH_2Cl_2-MeOH 1:0 to 93:7) to provide the title compound: ES-MS: 448 $(M+H)^+$; analytical HPLC: t_{ret}= 2.48 minutes (Grad 2).

Example 163

Inhibition of PDK1 kinase by compounds of the present invention

Activity determinations of compounds of the preceding examples, using the testing method described above, with the following test compounds of formula (I) exhibit the following IC_{50} values for PDK1 inhibition:

Letter	IC_{50} range class
A	≤0.5 µM
B	more than 0.5 µM up to 1 µM

Example	IC_{50} µM
3	A
4	A
8	A
9	A
10	A
11	A
12	A
13	A
23	B
26	B
27	B
28	A
29	B
30	B
32	A

33	B
34	A
35	A
38	A

Example 164

Tablets 1 comprising compounds of the formula (I)

Tablets, comprising, as active ingredient, 50 mg of any one of the compounds of formula (I) mentioned in the preceding Examples **1-162** of the following composition are prepared using routine methods:

Composition:

Active Ingredient	50 mg
Wheat starch	60 mg
Lactose	50 mg
Colloidal silica	5 mg
Talcum	9 mg
Magnesium stearate	1 mg
	175 mg

Manufacture: The active ingredient is combined with part of the wheat starch, the lactose and the colloidal silica and the mixture pressed through a sieve. A further part of the wheat starch is mixed with the 5-fold amount of water on a water bath to form a paste and the mixture made first is kneaded with this paste until a weakly plastic mass is formed.

The dry granules are pressed through a sieve having a mesh size of 3 mm, mixed with a pre-sieved mixture (1 mm sieve) of the remaining corn starch, magnesium stearate and talcum and compressed to form slightly biconvex tablets.

Example 165

Tablets 2 comprising compounds of the formula (I)

Tablets, comprising, as active ingredient, 100 mg of any one of the compounds of formula (I) of Examples **1-162** are prepared with the following composition, following standard procedures:

Composition:

Active Ingredient	100 mg
Crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
Magnesium stearate	5 mg
	447 mg

Manufacture: The active ingredient is mixed with the carrier materials and compressed by means of a tabletting machine (Korsch EKO, Stempeldurchmesser 10 mm).

Example 166

Capsules

Capsules, comprising, as active ingredient, 100 mg of any one of the compounds of formula (I) given in Examples **1-162**, of the following composition are prepared according to standard procedures:

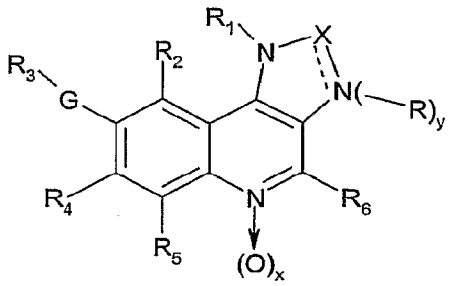
Composition:

Active Ingredient	100 mg
Avicel	200 mg
PVPPXL	15 mg
Aerosil	2 mg
Magnesium stearate	1.5 mg
	318.5 mg

Manufacturing is done by mixing the components and filling them into hard gelatine capsules, size 1.

What is claimed is:

1. A compound according to formula (I)



(I)

wherein

each of x and y is independently of the other 0 or 1,

R_1 is an organic moiety that can be bound to nitrogen,

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond the with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen; or

X is (CR_7), wherein R_7 is hydrogen or an organic or inorganic moiety with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero or y is 1 and then -R is $\rightarrow$O;

G is unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene; and

each of R_2, R_3, R_4, R_5 and R_6, independently of the others, is hydrogen, an organic moiety or an inorganic moiety;

or a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1,

wherein

each of x and y is, independently of the other, 0 or 1;

R_1 is substituted or unsubstituted aryl or heteroaryl, especially phenyl, which is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower

alkoxy; amino; amino-lower alkyl; amino-lower alkoxy; amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted, [e.g. -(C_1-C_7)NR_8R_9 or -O-(C_1-C_7)NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl), lower cycloalkyl (e.g. cyclopropyl) or R_8 and R_9, together with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)]; amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; heterocyclyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl, azetidinyl, pyridyl, piperidino, piperidyl, piperazinyl or lower alkyl-piperazinyl); wherein alkyl may be linear or cyclic (e.g. cyclopropyl) and the alkyl in any of the substituents above may optionally be substituted with -NR_8R_9, wherein R_8 and R_9 are as defined above;

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond and with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen; or

X is (CR_7) wherein R_7 is hydrogen or an organic moiety, such as C_1-C_7lower alkyl; amino or amino-lower alkyl; wherein alkyl may be unsubstituted or substituted with halo (e.g. methyl, ethyl, propyl, trifluoromethyl); lower alkoxy (e.g. methoxy); or cycloalkyl (e.g. cyclopropyl); with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero, or y is 1 and then -R is $\rightarrow$O;

G is unsubstituted or substituted alkenylene (e.g. ethenylene), unsubstituted or substituted alkynylene (e.g. ethynylene);

R_2 is hydrogen;

R_3 is hydrogen; lower alkyl; halo (e.g. fluoro, chloro or bromo); lower alkoxy (e.g. methoxy); or unsubstituted or substituted C_5-C_{14}aryl (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); or a heteroaryl being unsubstituted or substituted by one or more, especially 1-4 substituents; pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g.

methoxy); halo (e.g. fluoro); or -NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl);

R_4 is hydrogen or halo (e.g. F or Cl);

R_5 is hydrogen; and

R_6 is hydrogen; amino; amino-lower alkyl or alkylamido (e.g. methylamido -NHC(O)-CH_3);

or a pharmaceutically acceptable salt thereof.

3. A compound of formula (I) according to claim 1 wherein

each of x and y is, independently of the other, 0 or 1;

R_1 is substituted or unsubstituted phenyl where the phenyl is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower alkoxy; *N*-lower alkyl amino alkyl (e.g. methyl aminoethyl, cyclopropyl aminoethyl); *N,N*-di-lower alkyl amino alkyl; methoxy amino; methoxy N-methyl amino; amino; amino-lower alkyl; amino-lower alkoxy; azetidinyl lower alkyl; pyrrolidinyl; *N*-lower alkyl sulfonamide alkyl (e.g. CH_3-NH_2- $S(O)_2$-alkyl); amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted [e.g. -$(C_1$-$C_7)NR_8R_9$ or -O-$(C_1$-$C_7)NR_8R_9$, wherein R_8 and R_9 can be the same or different and are independently H; lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or R_8 and R_9 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)]; amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; heterocyclyl-lower alkyl; lower alkyl piperazinyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl,

azetidinyl, pyridyl, piperidino, piperidyl, piperazinyl or lower alkyl-piperazinyl); substituted heterocyclyls such as pyrrolidin-2-one, oxazolidin-2-one, pyrrolidine-2,5-dione, piperazine-2-one and oxo-oxazolidinyl; wherein alkyl may be linear or cyclic (e.g. cyclopropyl) and the alkyl in any of the substituents above may optionally be substituted with $-NR_8R_9$, wherein R_8 and R_9 are as defined above;

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond and with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen; or

X is (CR_7), wherein R_7 is hydrogen or an organic moiety, such as C_1-C_7lower alkyl; amino; amino-lower alkyl; wherein the alkyl may be unsubstituted or substituted with halo (e.g. methyl, ethyl, propyl, trifluoromethyl); lower alkoxy (e.g. methoxy); or cycloalkyl (e.g. cyclopropyl); with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero, or y is 1 and then -R is $\rightarrow O$;

G is unsubstituted or substituted alkenylene (e.g. ethenylene), unsubstituted or substituted alkynylene (e.g. ethynylene);

R_2 is hydrogen;

R_3 is hydrogen; lower alkyl; halo (e.g. fluoro, chloro or bromo); lower alkoxy (e.g. methoxy); or unsubstituted or substituted C_5-C_{14}aryl (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); or a heteroaryl being unsubstituted or substituted by one or more, especially 1-4, substituents independently selected from the group consisting of the substituents defined above under "substituted"; especially being pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g. methoxy); halo (e.g. fluoro); or $-NR_8R_9$, wherein R_8 and R_9 can be the same or different and are independently H, lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl);

R_4 is hydrogen or halo, (e.g. F or Cl);

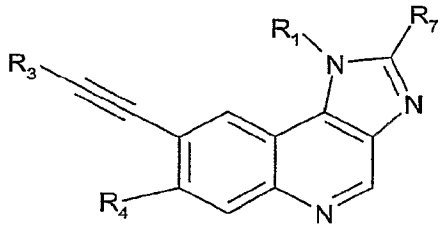
R_5 is hydrogen; and

R_6 is hydrogen; amino; amino-lower alkyl or alkylamido (e.g. methylamido -NHC(O)-CH_3);

or a pharmaceutically acceptable salt thereof as such, or

especially for use in the diagnostic or therapeutic treatment of a warm-blooded animal, especially a human.

4. A compound of formula (Ia)



(Ia)

wherein

R_1 is substituted or unsubstituted phenyl where the phenyl is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower alkoxy; amino; amino-lower alkyl; amino-lower alkoxy; amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted [e.g. -(C_1-C_7)NR_8R_9 or -O-(C_1-C_7)NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H; lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or R_8 and R_9 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)]; amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; heterocyclyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl, azetidinyl, pyridyl, piperidino, piperidyl, piperazinyl or lower alkyl-piperazinyl); wherein alkyl may be linear or cyclic (e.g. cyclopropyl) and the alkyl in any of the substituents above may optionally be substituted with -NR_8R_9, wherein R_8 and R_9 are as defined above;

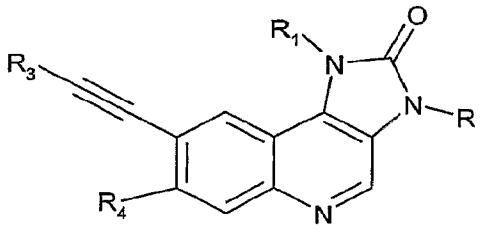
R_3 is hydrogen; lower alkyl; halo (e.g. fluoro, chloro or bromo); lower alkoxy (e.g. methoxy); or unsubstituted or substituted C_5-C_{14}aryl (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); or a heteroaryl being unsubstituted or substituted by one or more, especially 1-3 substituents; pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g. methoxy); halo (e.g. fluoro); or -NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H; lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl);

R_4 is hydrogen or halo, especially fluoro; and

R_7 is hydrogen or an organic moiety, such as C_1-C_7lower alkyl; amino or amino lower alkyl; where alkyl may be unsubstituted or substituted with halo (e.g. methyl, ethyl, propyl, trifluoromethyl); lower alkoxy (e.g. methoxy); or cycloalkyl (e.g. cyclopropyl);

or a pharmaceutically acceptable salt thereof.

5. A compound of formula (Ib)



(Ib)

wherein

R_1 is substituted or unsubstituted phenyl where the phenyl is substituted with up to 4, preferably up to 2 substituents, wherein the substituents are the same or different and are independently selected from halo (e.g. Cl or F); cyano; cyano lower alkyl (e.g. cyanomethyl, cyanoethyl and cyanopropyl); lower alkyl; lower alkoxy; amino; amino-lower alkyl; amino-lower alkoxy; amino-lower alkyl sulfanyl or thiol-lower alkyl; wherein the amino group can be mono or disubstituted, [e.g. -(C_1-C_7)NR_8R_9 or -O-(C_1-C_7)NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H; lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g.

cyclopropyl); or R_8 and R_9 together with the N atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl)]; amino-carbonyl-lower alkyl (e.g. R_8R_9-N-C(O)-CH_2-, wherein R_8 and R_9 are as defined above); heterocyclyl; heterocyclyl-lower alkyl; heterocyclyl-lower alkoxy or heterocyclyl-lower alkanesulfanyl wherein the heterocyclyl is a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. imidazolyl, imidazolinyl, pyrrolidinyl, morpholinyl, azetidinyl, pyridyl, piperidino, piperidyl, piperazinyl or lower alkyl-piperazinyl); wherein alkyl may be linear or cyclic (e.g. cyclopropyl) and the alkyl in any of the substituents above may optionally be substituted with -NR_8R_9, wherein R_8 and R_9 are as defined above;

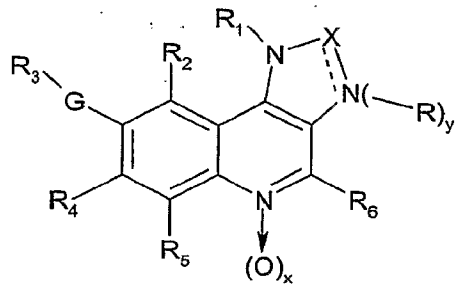
R_3 is hydrogen; lower alkyl; halo (e.g. fluoro, chloro or bromo); lower alkoxy (e.g. methoxy); or unsubstituted or substituted C_5-C_{14}aryl (e.g. phenyl, hydroxyphenyl, methoxyphenyl or aminosulfonyl-phenyl or benzo[1,3]dioxolo); or a heteroaryl being unsubstituted or substituted by one or more, especially 1-3, substituents; pyridyl (or an *N*-oxide of pyridyl) which is unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl (e.g. methyl); lower alkoxy (e.g. methoxy); halo (e.g. fluoro); or -NR_8R_9, wherein R_8 and R_9 can be the same or different and are independently H; lower alkyl (e.g. methyl, ethyl or propyl); lower cycloalkyl (e.g. cyclopropyl); or the R_8 and R_9 can, with the N atom, form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms (e.g. azetidinyl, pyrrolidinyl, piperidino, morpholinyl, imidazolinyl, piperazinyl or lower alkyl-piperazinyl);

R_4 is hydrogen or halo, especially fluoro; and

R is hydrogen or substituted or unsubstituted C_1-C_7lower alkyl; amino; mono or disubstituted amino; lower alkoxy (e.g. OCH_3) or cycloalkyl (e.g. cyclopropyl);

or a pharmaceutically acceptable salt thereof.

6. Use of a compound of the formula (I)



(I)

wherein

each of x and y is independently of the other 0 or 1;

R_1 is an organic moiety that can be bound to nitrogen;

X is C=O or C=S with the proviso that then the dashed line bonding X to N is absent, so that X is bound to the adjacent N via a single bond the with the proviso that then y is 1 and R is hydrogen or an organic moiety that can be bound to nitrogen; or

X is (CR_7), wherein R_7 is hydrogen or an organic or inorganic moiety with the proviso that then the dashed line bonding X to N is a bond, so that X is bound to the adjacent N via a double bond, and with the proviso that then y is zero or y is 1 and then -R is $\rightarrow$O;

G is unsubstituted or substituted alkenylene, unsubstituted or substituted alkynylene; and

each of R_2, R_3, R_4, R_5 and R_6, independently of the others, is hydrogen, an organic moiety or an inorganic moiety;

or a pharmaceutically acceptable salt thereof for treating a protein kinase dependent disease.

7. A use according to Claim 6, wherein the disease to be treated is a proliferative disease selected from a benign or malignant tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, or a tumor of the neck and head, an epidermal hyperproliferation, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, a mammary carcinoma, a leukemia, Cowden syndrome, Lhermitte-Dudos disease or Bannayan-Zonana syndrome.

8. Use of a compound according to formula (I) of claim 1 in the preparation of a pharmaceutical composition.

9. A pharmaceutical composition comprising a compound according to Claim 1.

10. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier material.

11. A compound according to Claim 1, selected from

2-[4-(8-Phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-{4-[8-(3-Methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-{4-[8-(4-Methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-{4-[8-(6-Methoxy-pyridin-3-ylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-[4-(8-Benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

4-{1-[4-(2-Amino-ethyl)-phenyl]-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide;

3-[4-(8-Phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine;

3-{4-[8-(4-Methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-propylamine;

3-{4-[8-(3-Methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-propylamine;

3-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine;

3-[4-(8-Benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine;

4-{1-[4-(3-Amino-propyl)-phenyl]-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide;

2-[4-(7-Chloro-8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-{4-[7-Chloro-8-(3-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-{4-[7-Chloro-8-(4-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-[4-(7-Chloro-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-[4-(7-Chloro-8-benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

4-{1-[4-(2-Amino-ethyl)-phenyl]-7-chloro-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide;

3-[4-(7-Chloro-8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine;

3-{4-[7-Chloro-8-(3-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-propylamine;

3-{4-[7-Chloro-8-(4-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-propylamine;

3-[4-(7-Chloro-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine;

3-[4-(7-Chloro-8-benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine;

4-{1-[4-(3-Amino-propyl)-phenyl]-7-chloro-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide;

2-[4-(7-Fluoro-8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-{4-[7-Fluoro-8-(3-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-{4-[7-Fluoro-8-(4-methoxy-phenylethynyl)-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-[4-(7-Fluoro-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-[4-(7-Fluoro-8-benzo[1,3]dioxol-5-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

4-{1-[4-(2-Amino-ethyl)-phenyl]-7-fluoro-1*H*-imidazo[4,5-*c*]quinolin-8-ylethynyl}-benzenesulfonamide;

2-[4-(2-Methyl-8-phenylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-{4-[8-(3-Methoxy-phenylethynyl)-2-methyl-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-{4-[8-(4-Methoxy-phenylethynyl)-2-methyl-imidazo[4,5-*c*]quinolin-1-yl]-phenyl}-ethylamine;

2-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-[4-(2-Ethyl-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

2-[4-(3-Propyl-8-pyridin-3-ylethynyl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

3-[4-(8-*trans*-Styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine;

2-[4-(7-Chloro-8-styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-ethylamine;

3-[4-(7-Chloro-8-styryl-imidazo[4,5-*c*]quinolin-1-yl)-phenyl]-propylamine;

2-{4-[8-(6-Fluoro-pyridin-3-ylethynyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-ethylamine;

2-{4-[8-(6-Morpholin-4-yl-pyridin-3-ylethynyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-ethylamine;

(5-{1-[4-(2-Amino-ethyl)-phenyl]-1H-imidazo[4,5-c]quinolin-8-ylethynyl}-pyridin-2-yl)-dimethyl-amine;

2-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethylamine;

2-[4-(2-Cyclopropyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethylamine;

2-[4-(2-Isopropyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethylamine;

Cyclopropyl-{2-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-amine;

Methyl-{2-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-amine;

1-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperidin-4-ylamine;

C-{1-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperidin-4-yl}-methylamine;

2-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethylamine;

N-Methyl-C-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-methanesulfonamide;

1-[4-(2-Azetidin-1-yl-ethyl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

8-Pyridin-3-ylethynyl-1-[4-(2-pyrrolidin-1-yl-ethyl)-phenyl]-1H-imidazo[4,5-c]quinoline;

[3-Chloro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[2-Chloro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[3-Methyl-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[2-Methyl-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[3-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

Dimethyl-{2-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-amine;

Dimethyl-{2-[4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-amine;

{2-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-ethyl}-dimethyl-amine;

{1-[4-(2-Dimethylamino-ethyl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinolin-2-yl}-dimethyl-amine;

1-[4-(4-Methyl-piperazin-1-yl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

2-Methyl-1-[4-(4-methyl-piperazin-1-yl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

1-[4-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

Dimethyl-{1-[4-(4-methyl-piperazin-1-ylmethyl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinolin-2-yl}-amine;

1-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

1-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-2-methyl-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

1-[3-Fluoro-4-(4-methyl-piperazin-1-yl)-phenyl]-2-methoxy-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

2-Methyl-1-(4-piperazin-1-yl-phenyl)-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

1-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-methyl-8-pyridin-3-ylethynyl-1H-imidazo[4,5-c]quinoline;

2-(4-Methyl-piperazin-1-yl)-5-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

2-(4-Methyl-piperazin-1-yl)-5-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

5-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(4-methyl-piperazin-1-yl)-benzonitrile;

5-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(4-methyl-piperazin-1-yl)-benzonitrile;

2-Piperazin-1-yl-5-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

5-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-piperazin-1-yl-benzonitrile;

5-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-piperazin-1-yl-benzonitrile;

5-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-piperazin-1-yl-benzonitrile;

3-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

3-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

3-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

3-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[4-(2-Ethyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

{4-[2-(3-Dimethylamino-propyl)-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile;

{4-[8-(6-Morpholin-4-yl-pyridin-3-ylethynyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile;

{4-[8-(1-Oxy-pyridin-3-ylethynyl)-imidazo[4,5-c]quinolin-1-yl]-phenyl}-acetonitrile;

[4-(4-Amino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[4-(4-Methylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetonitrile;

[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-acetonitrile;

2-Methyl-2-[4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile;

2-Methyl-2-[4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile;

2-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-2-methyl-propionitrile;

2-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-2-methyl-propionitrile;

2-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-2-methyl-propionitrile;

2-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-2-methyl-propionitrile;

3-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile;

3-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile;

3-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile;

3-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile;

1-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one;

1-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one;

1-[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one;

1-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-pyrrolidin-2-one;

1-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one;

1-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one;

1-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one;

1-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidin-2-one;

2-(2-Oxo-pyrrolidin-1-yl)-5-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

5-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile;

5-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile;

5-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-(2-oxo-pyrrolidin-1-yl)-benzonitrile;

3-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one;

3-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one;

3-[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one;

3-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-oxazolidin-2-one;

3-[4-(8-Pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one;

3-[4-(2-Methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one;

3-[4-(2-Methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-oxazolidin-2-one;

1-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione;

1-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione;

1-[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione;

1-[4-(2-Dimethylamino-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-2-fluoro-phenyl]-pyrrolidine-2,5-dione;

1-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione;

1-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione;

1-[2-Fluoro-4-(2-methoxy-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-pyrrolidine-2,5-dione;

4-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperazin-2-one;

1-Ethyl-4-[2-fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperazin-2-one;

1-Ethyl-4-[2-fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperazin-2-one;

1-Ethyl-4-[2-fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-piperazin-2-one;

4-[2-Fluoro-4-(8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-1-methyl-piperazin-2-one;

4-[2-Fluoro-4-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-phenyl]-1-methyl-piperazin-2-one;

2-Cyanomethyl-5-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

2-(Cyano-dimethyl-methyl)-5-(2-methyl-8-pyridin-3-ylethynyl-imidazo[4,5-c]quinolin-1-yl)-benzonitrile;

1-(4-Fluoro-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

1-(4-Ethyl-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

1-(3-Methoxy-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

1-(4-Methoxy-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

3-Methyl-8-pyridin-3-ylethynyl-1-(3,4,5-trimethoxy-phenyl)-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

2-Methyl-2-[4-(3-methyl-2-oxo-8-pyridin-3-ylethynyl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-propionitrile;

3-Methyl-1-[4-(2-oxo-oxazolidin-3-yl)-phenyl]-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

1-[3-Fluoro-4-(2-oxo-oxazolidin-3-yl)-phenyl]-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

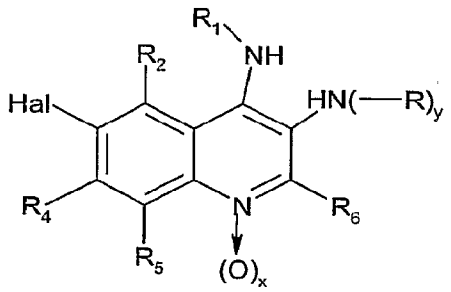
3-Methyl-1-(4-piperazin-1-yl-phenyl)-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

1-(3-Fluoro-4-piperazin-1-yl-phenyl)-3-methyl-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

3-Methyl-1-(4-methylamino-phenyl)-8-pyridin-3-ylethynyl-1,3-dihydro-imidazo[4,5-c]quinolin-2-one;

N-Methyl-N-[4-(3-methyl-2-oxo-8-pyridin-3-ylethynyl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]-acetamide; and pharmaceucially acceptable salts thereof.

12. A process to prepare a compound according to Claim 1, comprising reacting a compound of the formula (IIa)



(IIa)

with an alkenylene or alkynylene derivative;

and x, y, X, R_1, R_2, R_4, R_5, R_6 and R, are as defined in claim 1;

and, if desired, transforming an obtainable compound of formula (I) into a different compound of formula (I), transforming a salt of an obtainable compound of formula (I) into the free compound or a different salt, or an obtainable free compound of formula (I) into a salt; and/or separating an obtainable mixture of isomers of compounds of formula (I) into the individual isomers.

INTERNATIONAL SEARCH REPORT

I tional Application No
PCT/EP2004/013179

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/41 A61P35/00
//(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/058759 A (3M INNOVATIVE PROPERTIES COMPANY) 15 July 2004 (2004-07-15) Ex. 122, 147, 499, 505, 715, 821	1,6-10, 12
P,A	WO 03/097641 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; GARCIA-ECHEVERRIA, CARLOS; CAPRARO,) 27 November 2003 (2003-11-27) the whole document	1-12
A	US 6 331 539 B1 (CROOKS STEPHEN L ET AL) 18 December 2001 (2001-12-18) the whole document	1-12
A	US 5 605 899 A (GERSTER JOHN F 'US! ET AL) 25 February 1997 (1997-02-25) the whole document	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° *Special categories of cited documents:*

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2005	17/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fritz, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/013179

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 256 582 A (HOKURIKU SEIYAKU CO., LTD) 13 November 2002 (2002-11-13) the whole document	1-12
A	WO 02/46188 A (3M INNOVATIVE PROPERTIES COMPANY; CROOKS, STEPHEN L; GRIESGRABER, GEOR) 13 June 2002 (2002-06-13) the whole document	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

tional Application No
PCT/EP2004/013179

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004058759 A	15-07-2004	WO 2004058759 A1	15-07-2004
		US 2004147543 A1	29-07-2004
WO 03097641 A	27-11-2003	CA 2485012 A1	27-11-2003
		WO 03097641 A2	27-11-2003
		EP 1509521 A2	02-03-2005
US 6331539 B1	18-12-2001	AU 772179 B2	08-04-2004
		AU 5328400 A	02-01-2001
		BR 0011433 A	05-03-2002
		CA 2376305 A1	21-12-2000
		CN 1354663 A	19-06-2002
		CZ 20014363 A3	13-03-2002
		EE 200100669 A	17-02-2003
		EP 1198233 A1	24-04-2002
		HR 20010890 A1	31-08-2003
		HU 0201431 A2	28-08-2002
		JP 2003501474 T	14-01-2003
		MX PA01012547 A	14-10-2003
		NO 20015502 A	07-02-2002
		NZ 515967 A	31-10-2003
		PL 352554 A1	25-08-2003
		SK 17922001 A3	04-04-2002
		TR 200103575 T2	21-06-2002
		WO 0076519 A1	21-12-2000
		US 2004029877 A1	12-02-2004
		US 2003130299 A1	10-07-2003
		US 2004204438 A1	14-10-2004
		AU 766565 B2	16-10-2003
		AU 5328100 A	02-01-2001
		AU 773113 B2	20-05-2004
		AU 6334900 A	02-01-2001
		BR 0011448 A	14-12-2004
		BR 0014214 A	08-09-2004
		CA 2376296 A1	21-12-2000
		CA 2376304 A1	21-12-2000
		CN 1353609 A	12-06-2002
		CN 1355701 A	26-06-2002
		CZ 20014364 A3	13-03-2002
		EE 200100668 A	17-02-2003
		EE 200100670 A	17-02-2003
		EP 1198232 A1	24-04-2002
		EP 1187613 A1	20-03-2002
		EP 1438958 A1	21-07-2004
		HR 20010888 A1	31-08-2003
		HR 20010889 A1	31-08-2003
		HU 0201664 A2	28-08-2002
		HU 0202254 A2	28-10-2002
		JP 2003501466 T	14-01-2003
		JP 2003501473 T	14-01-2003
		MX PA01012508 A	02-07-2002
		NO 20015503 A	08-02-2002
		NO 20015504 A	07-02-2002
US 5605899 A	25-02-1997	US 5389640 A	14-02-1995
		US 5977366 A	02-11-1999
		US 2003119861 A1	26-06-2003
		US 6348462 B1	19-02-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/013179

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5605899 A		US 2003212270 A1	13-11-2003
		US 2004122231 A1	24-06-2004
		US 5741909 A	21-04-1998
		US 2002115861 A1	22-08-2002
		AT 179711 T	15-05-1999
		AT 229943 T	15-01-2003
		AU 658621 B2	27-04-1995
		AU 1566992 A	06-10-1992
		AU 673309 B2	31-10-1996
		AU 2715795 A	21-09-1995
		CA 2104782 A1	02-09-1992
		CA 2289219 A1	02-09-1992
		CZ 9301788 A3	18-10-1995
		DE 69229114 D1	10-06-1999
		DE 69229114 T2	04-11-1999
		DE 69232878 D1	30-01-2003
		DE 69232878 T2	20-11-2003
		DK 582581 T3	08-11-1999
		DK 872478 T3	31-03-2003
		EP 0582581 A1	16-02-1994
		EP 0872478 A2	21-10-1998
		ES 2131070 T3	16-07-1999
		ES 2186034 T3	01-05-2003
		HU 67026 A2	30-01-1995
		HU 211242 B3	28-11-1995
		HU 220667 B1	29-04-2002
		HU 222247 B1	28-05-2003
		HU 222251 B1	28-05-2003
		HU 222250 B1	28-05-2003
		IE 920605 A1	09-09-1992
		IE 990988 A1	13-12-2000
		IL 101110 A	08-12-1995
		IL 114570 A	31-10-1996
		JP 2955019 B2	04-10-1999
		JP 6504789 T	02-06-1994
		KR 235389 B1	15-12-1999
		NO 933069 A	01-11-1993
		NZ 241784 A	27-06-1995
		PH 31614 A	12-01-1999
		SG 46492 A1	20-02-1998
		SG 70625 A1	22-02-2000
		WO 9215582 A1	17-09-1992
		ZA 9201540 A	25-11-1992
EP 1256582 A	13-11-2002	AU 3058401 A	20-08-2001
		BG 107067 A	30-09-2003
		BR 0108303 A	05-03-2003
		CA 2399136 A1	16-08-2001
		EP 1256582 A1	13-11-2002
		HU 0204474 A2	28-04-2003
		MX PA02007525 A	13-12-2002
		NO 20023750 A	07-10-2002
		SK 11202002 A3	04-03-2003
		US 2004054182 A1	18-03-2004
		CN 1422269 A	04-06-2003
		CZ 20022626 A3	12-02-2003
		WO 0158900 A1	16-08-2001
		JP 2002161095 A	04-06-2002

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/013179

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1256582 A		PL 355866 A1	31-05-2004
		ZA 200206698 A	21-08-2003
WO 0246188 A	13-06-2002	AU 3061802 A	18-06-2002
		AU 3248202 A	18-06-2002
		AU 3249702 A	18-06-2002
		AU 3951602 A	18-06-2002
		AU 3951702 A	18-06-2002
		AU 3953002 A	18-06-2002
		BR 0116026 A	21-12-2004
		BR 0116047 A	30-09-2003
		CA 2430844 A1	13-06-2002
		CA 2431151 A1	13-06-2002
		CA 2436846 A1	13-06-2002
		CA 2436980 A1	13-06-2002
		CA 2436983 A1	13-06-2002
		CA 2436984 A1	13-06-2002
		CN 1479738 A	03-03-2004
		CN 1487939 A	07-04-2004
		CN 1479739 A	03-03-2004
		CZ 20031560 A3	12-05-2004
		CZ 20031561 A3	14-04-2004
		CZ 20031562 A3	17-03-2004
		CZ 20031563 A3	18-02-2004
		CZ 20031591 A3	12-11-2003
		CZ 20031592 A3	14-01-2004
		EE 200300268 A	15-10-2003
		EE 200300270 A	15-10-2003
		EE 200300271 A	15-10-2003
		EE 200300272 A	15-10-2003
		EE 200300274 A	15-10-2003
		EE 200300275 A	15-10-2003
		EP 1341789 A2	10-09-2003
		EP 1341790 A2	10-09-2003
		EP 1341791 A2	10-09-2003
		EP 1339715 A2	03-09-2003
		EP 1341792 A2	10-09-2003
		EP 1343784 A2	17-09-2003
		HR 20030461 A2	30-06-2004
		HR 20030462 A2	30-04-2004
		HR 20030463 A2	30-04-2004
		HR 20030464 A2	30-06-2004
		HR 20030466 A2	30-06-2004
		HR 20030467 A2	30-04-2004
		HU 0400704 A2	28-06-2004
		HU 0400710 A2	28-06-2004
		JP 2004532810 T	28-10-2004